OCT 23 1950

VOLUME 87

HOSPITAL LIBRARY

NUMBER 4

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

October, 1950

Studies of Respiratory Air Flow. II. Observations on Patients with Pulmonary Disease. Donald F. Proctor, Janet B. Hardy, and Ross McLean 225

A Unique Case of Obstruction of the Inferior Vena Cava. Ivan L. Bennett, Jr. 290

A Clinical Classification of Vestibular Disorders with Differentiation of Three Syndromes and Discussion of a Common Form of Vertigo Induced by Sudden Movement of the Head. Frank R. Ford 299

The Differentiation between Extrahepatic and Intrahepatic Obstruction of the Portal Circulation. A Clinical Study of the "Banti Syndrome." Oscar D. Ratnoff, C. Lockard Conley, and Morgan Berthrong 305

The Effect of Certain Cinchoninic Acid Derivatives on the Renal Tubular Secretion of Phenol Red. Earl H. Dearborn 328

Book Reviews 338

Books Received for Review 346

PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore-18, Maryland

Made in United States of America

Copyright, 1950, by The Johns Hopkins Press

BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

MANAGING EDITOR, FREDERIK B. BANG

ASSOCIATE MANAGING EDITOR, H. WILLIAM SCOTT, JR.

EDITORIAL BOARD

E. Cowles Andrus
Charles R. Austrian
Kenneth C. Blanchard
Edward M. Hanrahan
John Eager Howard
Arnold R. Rich

All correspondence relating to the publication of papers should be addressed to The Editor, Bulletin of The Johns Hopkins Hospital, Baltimore-5, Md.

Books for review should be sent to The Editor at the above address.

Twenty-five reprints, without covers, of articles will be furnished to contributors free of cost. An order slip for additional reprints, with a table showing cost, is sent with proof.

Correspondence concerning business matters should be sent to The Johns Hopkins Press, Baltimore-18, Maryland, U. S. A.

This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should any issue of the current volume be out of print at the time the subscription order is received, the pro rata value of such numbers will be credited to the next volume, and the renewal invoice therefore adjusted accordingly.

Subscriptions should be renewed promptly. To avoid a break in your series, subscriptions should be renewed promptly. The publisher cannot guarantee to supply back issues on belated renewals.

Subscriptions, new or renewal, may be sent to the Publishers or ordered through your agent.

Subscriptions in the British Empire except Canada may be sent to: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, London, W.C. 2.

THE JOHNS HOPKINS PRESS
BALTIMORE-18, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Post Office. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorised on July 3, 1918.

STUDIES OF RESPIRATORY AIR FLOW

II. Observations on Patients with Pulmonary Disease

DONALD F. PROCTOR, JANET B. HARDY, AND ROSS McLEAN

Departments of Otolaryngology, Pediatrics and Medicine (Physiological Division) of the Johns Hopkins University School of Medicine and the Johns Hopkins Hospital

Received for publication May 15, 1950

This is the second of a series of reports of studies of respiratory air flow in the evaluation of respiratory function in health and disease. The first report was devoted to analysis of the pneumotachogram in the normal subject (1).

A century ago such workers as Carson (2), Heynsius (3), and others studied the forces involved in respiration. Rohrer's (4) work over 25 years ago provided the first comprehensive study of the coordinated effect of these forces on respiration. Since that time improvements in methods have made possible such accurate and detailed studies as those of Neergaard and Wirz (5), Fleisch (6), and Vuilleumier (7). It is now possible to use measurements of intrapleural pressure, air flow velocity, and pressure gradients to analyse respiratory function.

From the clinical viewpoint measurements of respiratory function are carried out to help establish a proper diagnosis and prognosis and to determine suitability for and probable success of various forms of therapy. From the physiological and pathological viewpoint special emphasis is placed on an understanding of the function of the various parts of the respiratory apparatus in order to arrive at a clear idea of the mechanics of respiratory function and the pathogenesis of disease involving the respiratory system. The work reported herein is chiefly concerned with these measurements as they apply to the exchange of gases between the alveoli and the ambient atmosphere. The apparatus and the methods employed are described in Figure 1. Studies of forty seven patients are included in this report. Their ages and pathological conditions are indicated in table 1. The methods of study have included

This work has been supported by Grants in Aid from the U. S. Public Health Service. Work done with the technical assistance of Mary N. Linderman and Edith Keavney.

the pneumotachogram, alveolar-atmosphere pressure gradient studies, and spirometry.

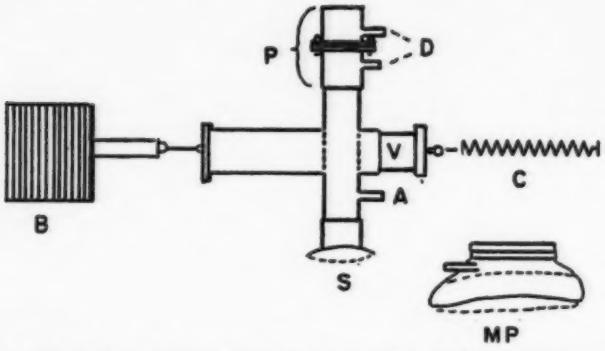


FIG. 1. Illustration of apparatus in the first article of this series was published incomplete by an oversight and is herein shown complete.

APPARATUS FOR AIR FLOW STUDIES

S. Mouthpiece for subject

A. Connection with strain gage for recording Alveolar Pressure

V. Sliding valve for obstructing air flow, closed by solenoid (B) and opened by coil spring (C)

P. Pneumotachometer with monel mesh screen

D. Connections to differential strain gage for recording pressure gradient representing flow velocity

Connections to strain gages are 4 cm. or less in length

Pressures are photographically recorded through Hathaway Amplifiers and Hathaway O.D. Galvanometers (frequency 150 cycles).

Resistance of this pneumotachometer is 0.05 cm. H_2O per liter per minute flow velocity. (0.087 at 300 liters per minute). Dead space of the apparatus 30 cc. for recording of alveolar pressure and 90 cc. altogether.

In high velocity studies a mask pneumotachometer has been used (MP) with a resistance of 0.013 cm. H_2O per liter per minute flow (0.015 at 300 liters per minute).

METHODS

Pneumotachograms were recorded using a monel mesh type of pneumotachometer with low resistance (0.087 cms. of water pressure per liter per minute flow except in the case of certain studies of very high velocities when a resistance of 0.013 cms. of water pressure was used). The alveolar-atmosphere pressure gradients were

measured by the methods of Vuilleumier (12). This method utilizes the pressure change which occurs at the mouth when air flow is suddenly and briefly interrupted. As demonstrated by Otis and Proctor (13), because of the relatively large volume of gas in the alveoli, this pressure change approximates very closely the gradient existing just prior to the interruption of flow. Pressures were measured by Statham type strain gage manometers and recorded optically through galvanometers with a frequency of 180–250 cycles per second.

A commonly used descriptive terminology for the pneumotachogram will facilitate discussions on the subject. Such a terminology should be based on the three

TABLE 1

Age of Subjects and Type of Pulmonary Disease

	AGE (YEARS)								
	3–9	10–14	15–20	21–30	31–40	41–50	51–60	61–70	Total
Normal (symptoms only)		1							1
Parenchymal disease, relatively normal respiratory function				1	1				2
Asthma with infection				1	3	1			5
Asthma without infection	2						2		4
Emphysema mild						2	1	1	4
Emphysema severe							3	2	5
Bronchiectasis bilateral	1			1	1	2			5
Bronchiectasis unilateral	1		1						2
Bilateral partial pulmonary resection	1								1
Unilateral partial or total pulmonary resection	4	1	4						9
Miscellaneous		1			4	1	2	1	9
Total	9	3	5	3	9	6	8	4	47

Under "miscellaneous" are listed two patients with cardiac disease and pulmonary symptoms and two with pulmonary fibrosis.

All patients who had pulmonary resection suffered from bronchiectasis.

factors which compose the pneumotachogram: Velocity, Time, and Acceleration. The letters V, T, and A should be used to indicate each of these factors and suitable subscripts to place them on the pattern under discussion. Definitions of the terms used in this report are as follows:

V_I Zero velocity just before inspiration

V_E Zero velocity just before expiration

V_{EP} Point of highest velocity during expiration

V_{DP} First point in inspiration when velocity increase in succeeding 0.1 second is less than ½ that in the preceding 0.1 second.

V_{OP}	Point at which velocity decrease in inspiration in succeeding 0.1 second is more than twice that in preceding 0.1 second.
A_{EEP}	Slope of line from V_E to V_{EP} expressed in ccs. per (0.1 sec.)^2
A_{EPI}	Slope of line from V_{EP} to V_I expressed in ccs. per (0.1 sec.)^2
A_{IDP}	Slope of line from V_I to V_{DP} expressed in ccs. per (0.1 sec.)^2

Other suggested terms and their definitions are listed in the first article in this series (1).

FORCES INVOLVED IN RESPIRATION

The movement of air in and out of the lungs results from a rhythmic, changing interplay of a variety of forces (fig. 2). A simple concept of the dynamic changes in these forces and their effects can be expressed in the following manner.

At the end of a quiet expiration the two chief forces acting when the lungs are at rest, those of chest and lung elasticity, are equal and exerted in opposite directions. When the force of the inspiratory muscles is also opposed to lung elasticity the lung expands and inspiration occurs. At the end of inspiration these muscles relax so that once again the two chief active forces are chest and lung elasticity. Lung elasticity now exerts a greater force because of the greater degree of expansion of the lungs, and contraction of the lungs producing expiration ensues and continues until that position is again reached where the forces exerted by chest and lung elasticity are equal and opposed.

In pulmonary disease any or all of these forces may be altered and the resulting change in respiratory balance alters the characteristics of air flow.

ELASTIC FORCES IN RESPIRATION

Elastic forces can be defined as the forces contained within a substance or tissue tending to return it to a given shape or size from a limited degree of distortion.

The forces of chest and lung elasticity vary dynamically with the state of expansion of the lungs. At the end of a maximum inspiration chest elasticity is working in an expiratory direction and lung elasticity is a very strong force working in the same direction. As air moves out of the lungs the force of lung elasticity diminishes (probably as a linear function of volume over the middle range of expansion (5)) and at a volume corresponding to about 70 per cent of the vital capacity

forces due to chest elasticity have become zero (8). At this point the chest wall itself is at its normal resting position. As more air is expired, chest elasticity begins to act as a force in the inspiratory direction,

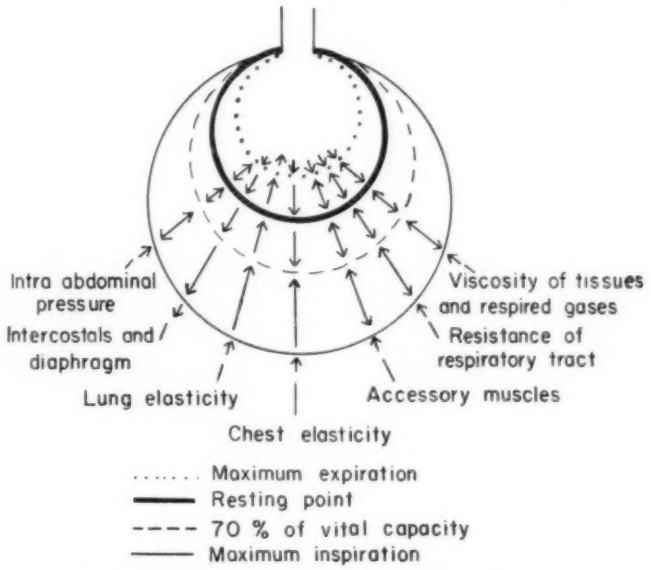


FIG. 2. Diagramatic illustration of the forces involved in pulmonary ventilation. The viscosity forces and the resistance of the respiratory tract to the passage of gases oppose ventilatory movement in either direction. Lung elasticity always opposes inspiratory movement and assists expiratory movement. The intercostals and diaphragm assist inspiration and offer little or no resistance to expiratory movements. Chest elasticity during quiet breathing assists inspiration and opposes expiration but when the lungs have been inflated to a volume greater than 70 per cent of vital capacity chest elasticity opposes further inflation and assists expiration down to this volume. There is insufficient information as to the relative strength of these forces but it is known that at the resting point in quiet breathing the force of chest elasticity equally opposes the force of lung elasticity.

and at the normal resting point for the chest wall and lungs this force is opposed to and equal to the force due to lung elasticity, still exerted in the expiratory direction. This is the point of inflation reached at the end of a normal quiet expiration. After maximum expiration,

lung elasticity is a relatively weak force but still acting in an expiratory direction and the force of chest elasticity is now acting strongly in an inspiratory direction. The strength of these forces in the inspiratory direction, after maximum expiration, is about equal to those in the expiratory direction after a maximum inspiration (1, 8).

It is possible to measure lung elasticity by simultaneously recording intrapleural pressure and the pneumotachogram (5, 9). Whenever air flow velocity is at zero the force exerted on the intrapleural space is that of lung elasticity. Under this circumstance the difference between intrapleural pressure and atmospheric pressure is a measure of the elastic tension of the lungs.

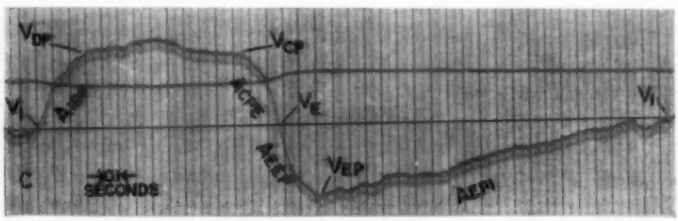


FIG. 3. Normal pneumotachogram. All recordings are made with the subject in the seated position.

EXPIRATORY PHASE OF THE PNEUMOTACHOGRAM

From experiments on normal subjects there is evidence (1) that during quiet breathing (fig. 3) the initial rise in air flow velocity at the start of expiration (A_{EEP}) is the result of the added force of lung elasticity opposing a somewhat decreased force of chest elasticity (corresponding to the increased lung volume) when inspiratory effort is terminated. The subsequent gradual fall in flow velocity until the end of expiration (A_{EPI}) is in turn a result of the reduction in this inequality between the two elastic forces as lung volume approaches the resting point (fig. 2). In the normal subject at rest, expiration is accomplished in large part without muscular effort.

In the study of 49 normal subjects, 50 per cent were found to have an expiratory pattern similar to that designated as type 1 (fig. 4A), 25 per cent of the normals had patterns similar to that designated as type 2 (fig. 4B), and 25 per cent similar to type 3 (fig. 4C).

Until a much larger number of normal subjects is studied and followed over a period of many years one cannot judge the significance of the differences between these patterns found in subjects who are normal as far as can be determined at the time of this study. Types 1 and 2 are characterized by a nearly dome shaped inspiratory phase

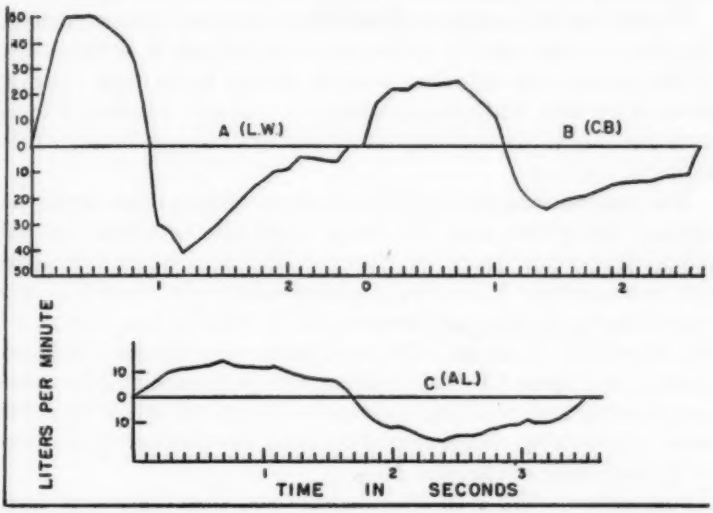


FIG. 4A. L. W., Female, white, 26 years old with pulmonary tuberculosis, cavitation and pneumothorax. Pneumotachogram resembling type 1, found in 50 per cent of normal subjects.

B, C. B., Male, white, 60 years old with pulmonary emphysema. Expiratory pattern resembling type 2, found in 25 per cent of normal subjects.

C, A. L., Female, white, 35 years old with spontaneous pneumothorax. Expiratory pattern resembling type 3, found in 25 per cent of normal subjects.

with a fairly rapid rise in velocity at the onset of inspiration a decrease in acceleration (or in some even a slight deceleration) after about one quarter to one third of inspiratory time. Nearly peak velocity is maintained until the lapse of about two thirds to three quarters of inspiratory time when velocity begins to fall towards zero. The expiratory phase in both of these types is roughly triangular in shape with a rapid rise in velocity at the onset of expiration and afterwards a gradual and

steady fall in velocity. In type 1 this fall continues steadily until zero flow is reached while in type 2, when the velocity is still about one tenth to one twentieth of peak expiratory velocity, flow is suddenly terminated and inspiration begun. Type 3 is characterized by a more gradual rise and fall in all phases of the pneumotachogram resulting in a shallow dome shaped curve both in inspiration and expiration.

Fourteen of the patients studied, 29 per cent, had patterns different from any of those found in the normal subjects; only 6, or 13 per cent, of the patients had expiratory patterns similar to the type 1 normal; 27 or 57 per cent, had patterns similar to type 2 or 3 normal. The following examples illustrate expiratory patterns not seen in any normal subjects.

The pneumotachogram of P.P. a patient suffering from severe pulmonary emphysema who, six months later, died of chronic cor pulmonale is shown in figure 5 C. This pattern demonstrates a prolonged time interval from V_{CP} to V_{EP}, relatively low velocity at V_{EP}, prolonged expiratory time, and irregular fall in velocity A_{EPI}. Figure 5 A is a record from a patient with severe pulmonary fibrosis of unknown etiology, and figure 5 B from a patient with long standing tuberculosis and bronchiectasis resulting in extensive destruction of one lung. The major abnormality demonstrated in these two respiratory patterns is the irregularity of the line A_{EPI}.

Four patients had such abnormalities and these have been interpreted as indicating loss of lung elasticity. A prolonged time interval from V_{CP} to V_{EP}, relatively low velocity at V_{EP}, relatively prolonged expiratory time, irregular fall in velocity A_{EPI} are all considered indications that the force of lung elasticity is impaired or absent and that it must be supplemented by respiratory muscles in order to produce expiration. This reasoning is based on the assumption that the normal expiratory pattern (best shown in fig. 4A) is a fairly simple reflection of the effect of elastic forces as inspiratory muscular effort ceases. It is also assumed that relaxation of inspiratory muscles probably begins at or shortly after the point designated as V_{CP}.

Eight of the patients showed an entirely different abnormality in the expiratory pattern (fig. 6). These patients suffered from chronic pulmonary infection (5 having bronchiectasis). The short time interval between V_{CP} and V_{EP}, the relatively high peak velocity V_{CP} would,

if the above reasoning is correct indicate good lung elasticity (fig. 6A and 6C). The gradual fall in velocity after V_{EP} is an indication of

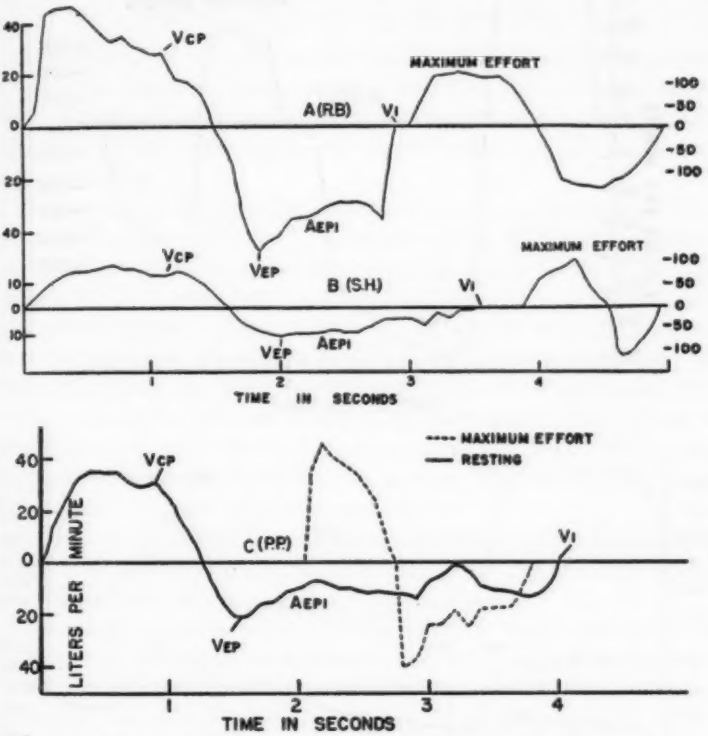


FIG. 5. The scale for velocity in maximum effort is on the right.

A, R.B., Patient with pulmonary fibrosis of unknown origin. Slightly dyspneic at rest.

B, S.H., Patient with pulmonary tuberculosis and bronchiectasis. Left lung, demonstrated by bronchospirometry, to be non-functioning. Moderate dyspnea on exercise.

C, P.P., A man with pulmonary emphysema and chronic cor pulmonale.

resistance to flow. This will be more fully considered in connection with the discussion of forces impeding air flow. Two patients (also with long standing but particularly severe bronchiectasis) had the same type of

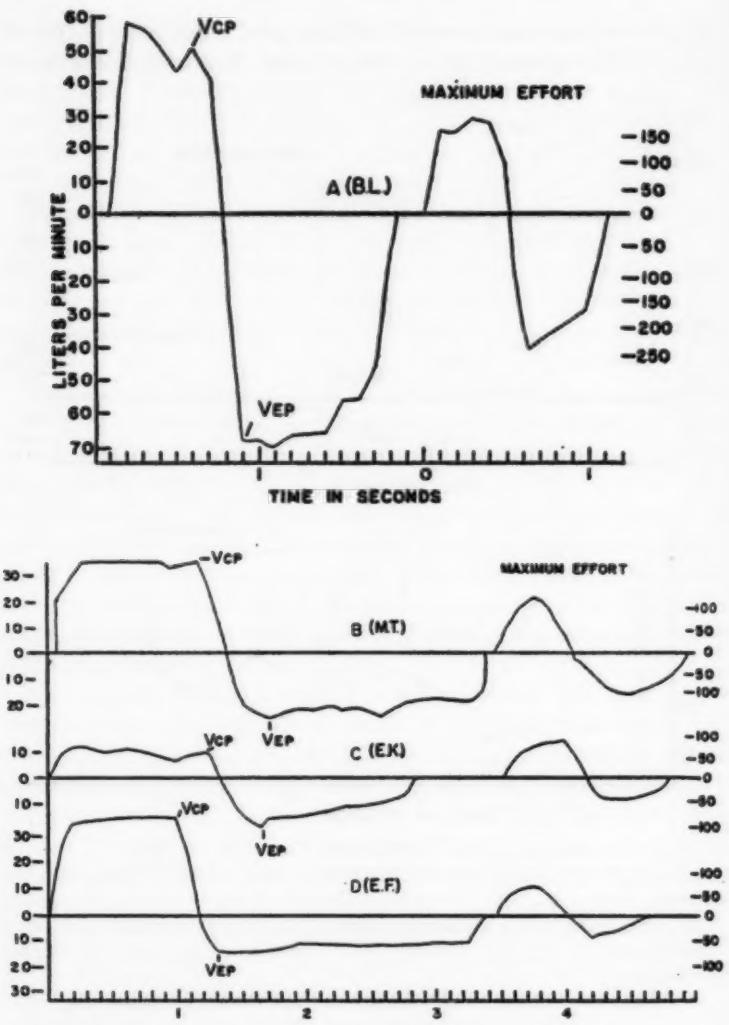


FIG. 6A, B.L., A young woman with multilobar bronchiectasis.
B, M.T., A middle aged woman with bronchectasis in all five lobes.
C, E.K., An adolescent girl with bilateral bronchiectasis.
D, E.F., A young woman with multilobar bronchiectasis.

pattern but V_{EP} was relatively low (fig. 6B and 6D). This may be attributable to some loss of lung elasticity.

INSPIRATORY PHASE OF THE PNEUMOTACHOGRAM

Since all but 6 of the patients had inspiratory patterns similar to that found in the normal subjects it would seem that this phase of respiratory air flow is less frequently disturbed (as reflected in the pneumotachogram) than is the expiratory phase in the forms of pulmonary disease studied.

Certain abnormalities in the inspiratory portion of the pneumotachogram are illustrated in figure 7. In one patient (fig. 7E) there is a sudden rise to a high flow velocity at the beginning of inspiration A_{IDP}. This patient suffered from asthma, bronchiectasis and emphysema, and had severe dyspnea at rest. There is also a post inspiratory pause. It is interesting that a similar A_{IDP} was seen in another patient (fig. 7B) with asthma on a functional basis and subjective dyspnea at rest.

The rectangular pattern, shown in figure 7A and 7C, was found in several patients with chronic pulmonary infection. The pattern shown in figure 7D was obtained from a patient with severe pulmonary fibrosis who was also somewhat dyspneic at rest.

It seems possible that the sudden rise in velocity at the beginning of inspiration as demonstrated in figure 7B and 7E results from violent inspiratory effort in response to the dyspnea.

A post inspiratory pause, as shown in figure 7E, (waste time from the point of view of respiratory efficiency) may also result from dyspnea.

The patterns shown in figure 7A and 7C may result from resistance to air flow and will be more fully discussed in the next section.

FORCES IMPEDING RESPIRATORY AIR FLOW

When a normal subject breathes against added resistance a characteristic change in respiratory pattern regularly occurs (1) (fig. 8A). The resistance must be sufficient to increase the alveolar pressure gradient (the gradient in pressure between the alveolus and the ambient air required to produce a given velocity of air flow in and out of the lungs) about 10 fold to produce this type of pattern although smaller resistances produce changes of lesser degree. The normal subject automatically shifts to a higher resting volume when breathing against added resistance (fig. 8B).

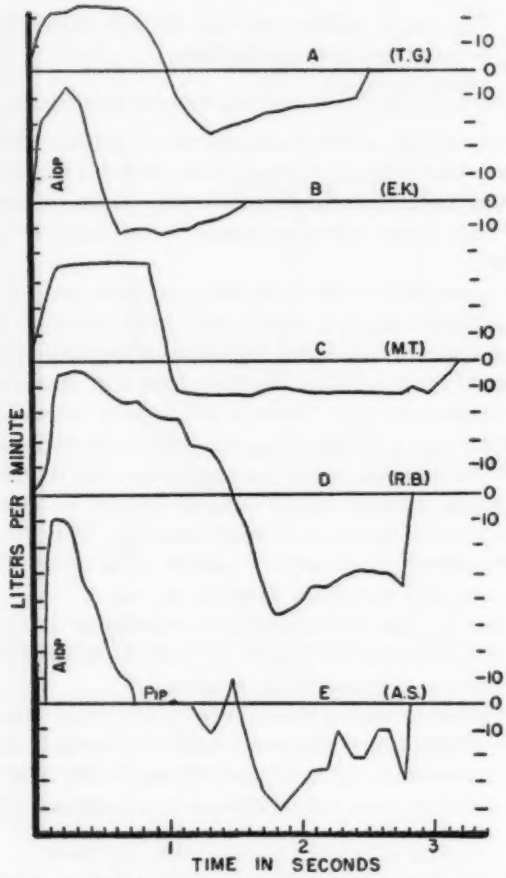
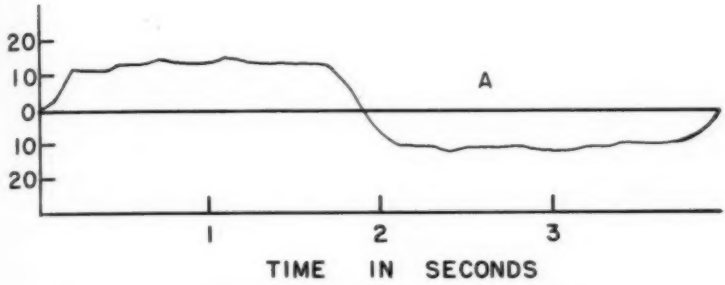


FIG. 7A, T.G., An elderly man with pulmonary fibrosis and emphysema.
E.K., A young woman with asthma on a functional basis.
C, M. T., A middle aged woman with bronchiectasis in all five lobes.
D, R. B., A young man with severe pulmonary fibrosis of unknown origin.
E, A. S., A young woman with severe asthma, bronchiectasis and emphysema.

To understand this type of "resistance" pattern one might consider a balloon filled with air to a certain degree of tension. When the neck is released there is a sudden outflow of air at high velocity and a rapid



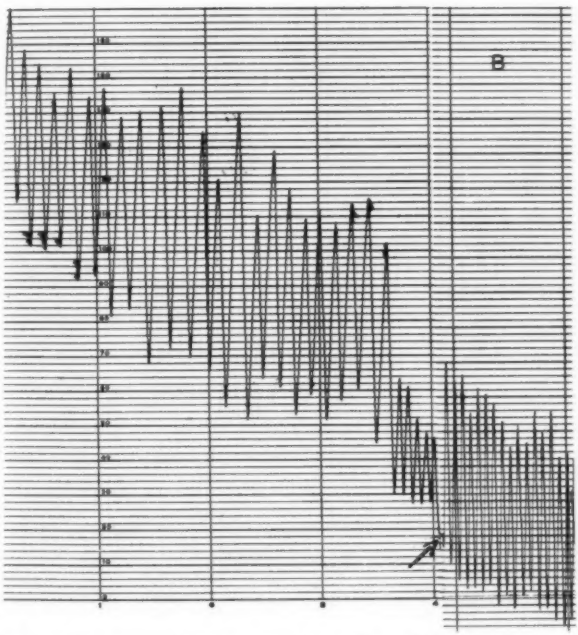


FIG. 8A. Pneumotachogram breathing against added resistance of 0.5 cms H_2O pressure per liter per minute flow. This record was taken on the same normal subject as the record shown in fig. 3.

B. Spirometric tracing on the same normal subject breathing against added resistance showing a rise of approximately 500 ccs. of residual volume when subject encounters this resistance. Read from right to left. Tracing at right is without resistance. Change to resistance is marked by arrow.

decline in velocity as the volume of the balloon and hence its elasticity decreases (fig. 9). When the neck of the balloon is partially obstructed the initial peak velocity is less, but since the volume and elastic force decreases more slowly the velocity of outflow decreases more slowly. A similar effect upon the pattern of outflow velocity would result if the viscosity of the contents of the balloon or the viscosity of the wall of the balloon were increased instead of placing a resistance at the neck.

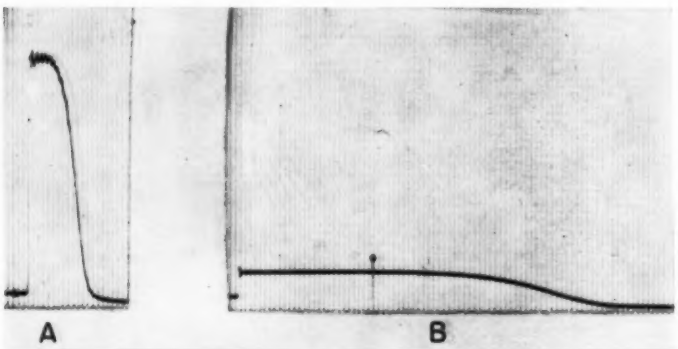


FIG. 9. The vertical lines mark 0.1 second intervals. Movement of tracing upwards indicates acceleration, downwards indicates deceleration.

A. Inflated balloon without obstruction at the neck. Rapid outflow of air and fall in velocity in flow of air.

B. Inflated balloon with resistance in the neck. Slower flow of air and fall in velocity of air flow.

The tendency to breathe with a larger reserve air when faced with added resistance brings into play a larger elastic force during expiration producing the sharp A_{EEP} seen in most of the patients with this type of pattern (fig. 6).

A pattern almost identical to the one produced in the normal subject when breathing against added resistance is seen in many patients with pulmonary disease (fig. 6). When the alveolar pressure gradients of these patients are studied one finds that in many these are no higher than the gradients in normal subjects at equal flow velocities and in none is the gradient more than 4 times that found in the average nor-

mal. If this pattern is the result of resistance to the forces producing air flow and the resistance met by the air itself is not markedly increased, the opposing force must lie in tissue viscosity. This would be in keeping with the pathological conditions involved in patients with severe bronchiectasis. The phrase "tissue viscance" as used herein refers to the viscous resistance to deformation of all or any of the structures contained within the chest (excluding air).

To measure the force required to overcome tissue viscance during respiration it is necessary to measure the total work of breathing, the work expended upon elastic forces and the work expended upon air. This has been done in one normal subject (10) and 15 per cent of the total work was found to be expended upon tissue viscance. More extensive studies now being carried on by Dr. Arthur Otis and associates at the University of Rochester indicate that the figure may be even lower than this (11). It is ordinarily impossible in the study of patients to obtain this information. It is possible to determine the resistance to air flow by a method first employed by Vuilleumier (12, 13). Such studies have been carried out on all but 2 of the patients included in this report.

For the purpose of discussion the normal alveolar-atmosphere pressure gradient relationship to flow velocity may be defined by an equation* derived from extensive studies in one normal subject. In this person a gradient of about 2 cms. H_2O pressure was required for a flow velocity of 30 liters per minute. Actually the average of 33 determinations on normal adults was 1.9 cms. H_2O pressure for this velocity, with a range of individual points from 0.5 to 3.8. The alveolar atmosphere pressure gradient was found to be approximately normal by this definition in 17 of the 47 patients studied. It is interesting to note that in this group are included 7 patients suffering from bronchiectasis, 2 patients with pulmonary fibrosis, and 1 with a relatively mild emphysema. The remaining 7 patients suffered from a variety of disorders including pleural effusion, mediastinal emphysema (healed) and spontaneous pneumothorax. A chart of pressures found in a group of normal subjects and patients is shown in figure 10.

* The equation derived is $\Delta P = 0.051\ V + 0.0007\ V^3$ where ΔP equals the pressure gradient between the alveolus and atmosphere, V is the velocity of flow of air corresponding to this gradient.

In no adult patient was this gradient found to be more than four times that seen in the normal subject, that is 8 cms. H_2O pressure for 30 liters per minute flow. Thirteen patients had pressures 3 to 4 times higher than normal. Three of these suffered from asthma, 2 from cardiac failure with dyspnea, 1 from congenital cystic disease of the lungs, 4 from bronchiectasis, 2 from emphysema, and 1 from spontaneous pneumothorax. Seventeen patients had pressures about twice as high as the average normal (fig 11).

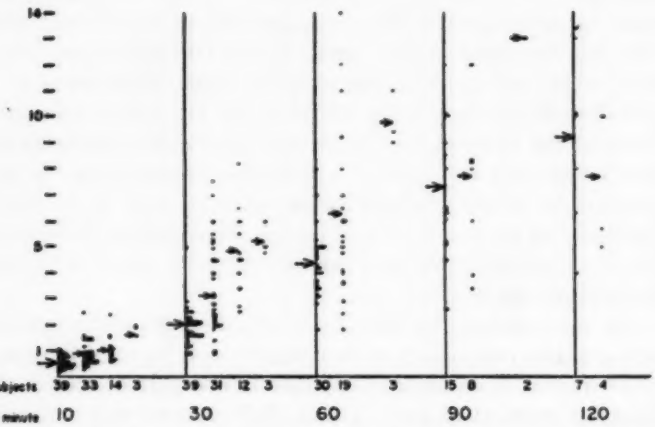


FIG. 10. Average pressure gradients for indicated velocities in patients and normals, children and adults. Measurements at high velocities were not obtainable on many; the numbers recorded are indicated in the chart. From left to right in each block are represented: adult normals, adult patients, children patients, and normal children. Figures on abcissae represent liters per minute. Figures on ordinate represent average alveolar pressure for indicated flow velocity given in cms. H_2O pressure. The arrows indicate the mean for each group.

The relationship between alveolar pressure and flow velocity in the normal subject approaches linearity at velocities up to 50 to 75 liters per minute. This signifies that at such velocities respiratory air flow occurs in a nearly streamlined fashion. The equation for this relationship is $\Delta P = K_1V + K_2V^{2*}$ (4, 12). Turbulence in normal respiratory air flow begins to be noticeable at about 50–75 liters per minute (14).

When air at a given temperature flows through a tube of given dimensions flow will be stream-lined until critical velocity is reached at

which time turbulence will begin to occur. As long as the flow is streamlined the pressure gradient along the tube will be proportional to the velocity, the relationship being defined by the equation $\Delta P = KV$. When flow is turbulent this relationship is altered and is now represented by the equation $\Delta P = KV^2$ (15).

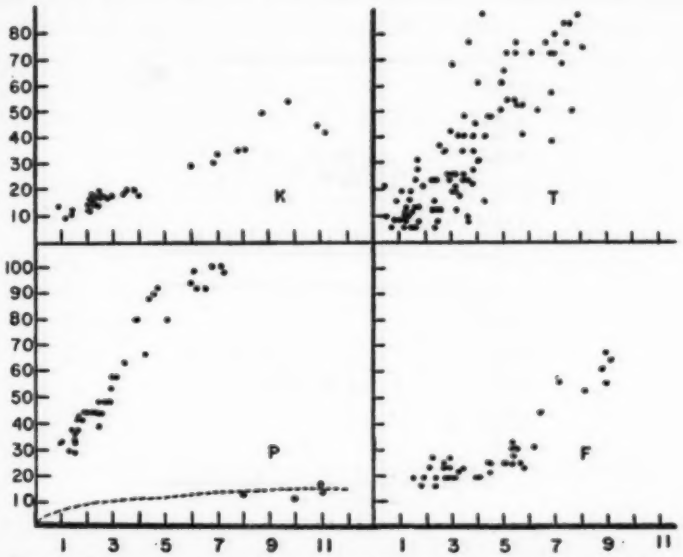


FIG. 11. These charts show the relationship between air flow velocities (in liters per minute) on the ordinates and air pressure gradients (in cms. H_2O) producing such flows, on the abcissae. Lower left is a normal subject, dotted line indicates the relationship with added resistance of 0.5 cms. H_2O per liter per minute flow. Most of the points recorded under these conditions show pressures too high to be recorded on this chart. The three other charts are on patients with long standing diffuse bronchiectasis.

In many patients the pattern of relationship between alveolar pressure and flow velocity indicates the development of turbulence at velocities of only 20 to 30 liters per minute (fig. 12). This is especially so in children but has been noted to a lesser degree in some adults. It seems probable that although the patients studied do not have severe resistance offered to air flow in their respiratory tracts when ventilation is moderate, in many the resistance is of such a character that turbulent

flow at relatively low velocites offers a severe impediment to the production of high velocities during maximum ventilatory effort. More will be said of this in connection with the discussion of ventilatory reserve.

A higher resistance to expiratory then inspiratory air flow has been clearly demonstrated by alveolar pressure studies in only 4 patients,

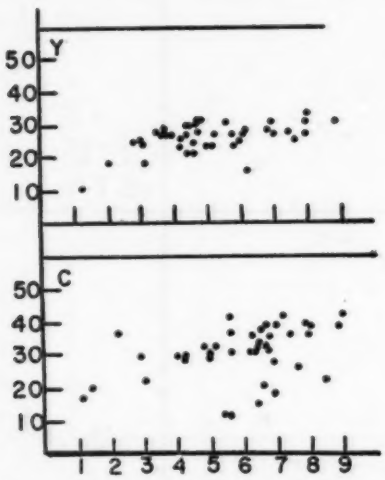


FIG. 12. Alveolar pressure charts showing increasing pressure gradients at low flow velocities with very slight increase in flow. In these 2 individuals turbulence seems to develop in respiratory air flow at velocities of about 30 liters per minute. Velocity in liters per minute on the ordinates, alveolar pressure in cms. H_2O on the abcissae.

(such a difference has not been found in any normal subject). One of these patients was a man suffering from pulmonary emphysema (fig. 13). Another had emphysema, and the remaining 2 had bronchial asthma. In 5 other patients a less well marked difference was found. Too few patients with typical pulmonary emphysema or bronchial asthma have been studied to draw definite conclusions on this point.

VENTILATORY RESERVE

Studies of respiratory air flow through the pneumotachogram and measurements of the alveolar pressure gradient throw some light on the

manner in which ventilatory reserve may be limited in patients with pulmonary disease.

Maximum breathing capacity is measured by having the subject attempt to voluntarily produce a maximum ventilation of his lungs for a twenty second period. This is expressed in liters per minute. The ventilatory reserve is the maximum breathing capacity minus the resting ventilation expressed in liters per minute. It represents the capacity for ventilation which may be voluntarily employed in excess of the resting ventilatory requirement. It is usually expressed in terms of percentage of the maximum breathing capacity. For example, if

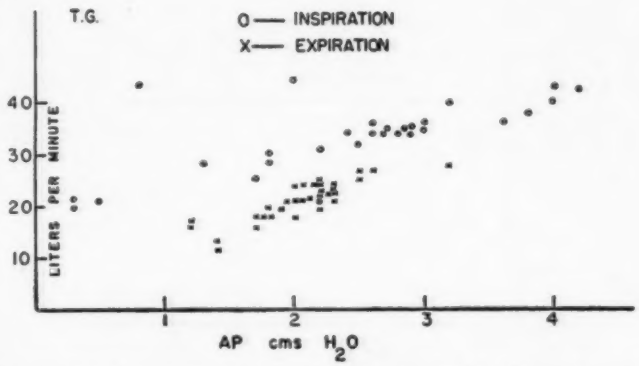


FIG. 13. Alveolar pressure chart of an elderly man (T.G.) with emphysema demonstrating higher expiratory pressures than those found on inspiration.

the maximum breathing capacity is 100 liters per minute and the resting minute volume is 5 liters per minute, the ventilatory reserve is 95 liters per minute or 95 per cent. The normal ventilatory reserve is greater than 95 per cent. When it falls to the level of 70 per cent, no satisfactory tolerance to exercise may be expected to exist and prolonged dyspnea is the almost invariable result of even relatively mild exercise.

One can think of the patient's maximum ventilatory capacity in relation to any given period of time from a single breath to many hours. From a practical viewpoint one is interested in two things:—how much air can be moved in and out of the lungs as rapidly as possible, and how long this effort can be maintained. The ability to move air in and

out of the lungs as rapidly as possible can be readily studied in detail by means of the pneumotachogram during maximum voluntary effort.

A single violent expiratory puff is best produced after a very deep inspiration and the reverse is true of an inspiratory gasp (fig. 14). When an expiration begins after a maximum inspiration the respiratory

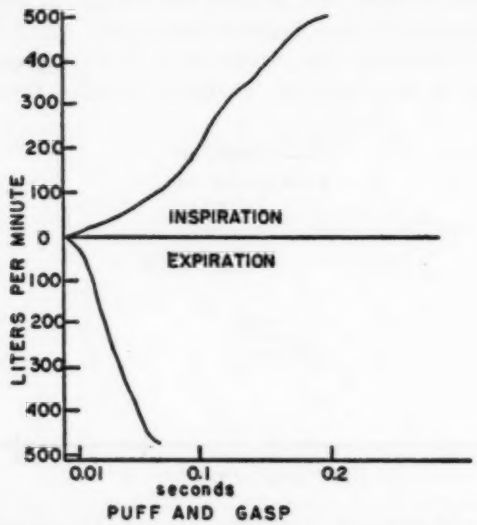


FIG. 14. Inspiratory gasp accomplished by maximum effort after deep expiration. Expiratory puff accomplished by maximum effort after deep inspiration. These charts are drawn from records on a normal subject.

muscles are supplemented by the elastic tension of the lungs and chest wall. In the normal subject very high peak flows (300 to 400 liters or more per minute) are reached rapidly;* but as lung volume decreases elastic tension falls off and chest wall elasticity opposes expiratory effort. The position of the respiratory muscles also passes the point at which they may act with the greatest effectiveness. Within about

* Similar studies reported in the first of this series of articles were carried out with a pneumotachometer with slightly higher resistance than that used in these studies. Hence the somewhat different results reported here.

0.1 seconds, or after the expiration of less than 10 per cent of the vital capacity, flow acceleration decreases and deceleration begins. A similar series of events occurs in inspiratory gasps but here peak velocity is reached more slowly and with a somewhat different pattern.

If the velocity of air flow rises lineally from zero to 400 liters per minute in 0.1 seconds, lung volume has been altered by about 330 ccs; and for each 0.1 seconds that this peak velocity is maintained there is a further alteration in lung volume of 660 ccs. One cannot possibly perform maximum ventilation rates using tidal volumes as large as the vital capacity, since by the time 50 per cent of the vital capacity has been expired or inspired, flow velocity has fallen well below peak and the remainder is moved at a relatively low speed. What proportion of the vital capacity may best be used will depend on the peak velocity the subject can attain, how rapidly it is reached and how long it can be maintained, as well as the rapidity with which inspiratory effort can be terminated and expiration begun. The maximum ventilation capacity will depend on these factors among others, the relative speed with which the inspired volume can be expired and the ability to maintain the violent muscular effort required over given periods of time.

In considering limitations of ventilatory reserve in patients it is well to remember that average air flow velocity is twice the maximum breathing capacity. When half of the respiratory cycle is occupied by expiration an average flow velocity of 200 liters per minute would be required to produce a maximum breathing capacity of 100 liters per minute. Among the normal subjects the average peak flow velocity during maximum effort was found to be 54 per cent higher than the average of the peak flows obtained during maximum effort by patients with pulmonary disease.

Added resistance to breathing radically curtails the subject's ability to increase ventilation with maximum effort. Added resistance of 0.013 cms. H_2O per liter per minute flow (that of the pneumotachometer itself) and 0.1, 0.15, 0.36, and 0.5 cms. H_2O per liter per minute flow were studied in a normal subject (fig. 15). With the highest of these resistances this subject's maximum ventilatory capacity (as measured through the maximum effort pneumotachogram) is 30 per cent of his capacity with the resistance of the pneumotachometer alone. The low

resistance of 0.1 cm. of H_2O per liter per minute flow reduced the maximum ventilatory capacity to about 70 per cent of the subject's normal. Even a pneumotachometer with a slightly higher resistance than the one ordinarily used in these studies of maximum effort (0.087 cms. H_2O per liter per minute compared to 0.013; 17 cms. H_2O pressure compared to 3 cms. H_2O pressure per 200 liters per minute flow) reduces peak flow velocities to 60 per cent of those otherwise attained.

The position of the subject has surprisingly little effect on the maximum effort pneumotachogram (fig. 16). The patterns while seated and

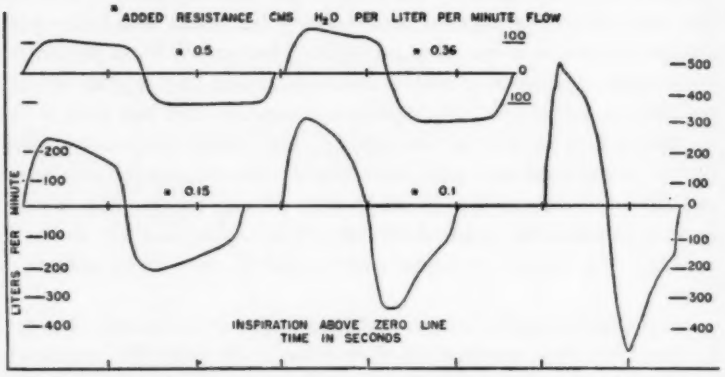


FIG. 15A. Maximum effort pneumotachogram on a normal subject showing alteration in pattern with added resistances as indicated.

standing are almost identical. Slightly smaller flow velocities are reached while lying supine.

Patients with pulmonary disease show three main variants from the normal in the pattern of breathing during maximum effort.

1. Although with maximum effort nearly all patients are able to reach their peak flow velocities as rapidly or almost as rapidly as the normal subjects, these peaks are commonly much lower than those found in the normal (fig. 17). As an example, M.L. in one maximum effort cycle required 1.0 second to inspire 841 ccs. In one normal subject exactly the same volume was inspired in 0.2 seconds. The major difference in this regard between these 2 individuals lay in the different ability to produce high flow velocities. M.L., figure 17A, was one of the

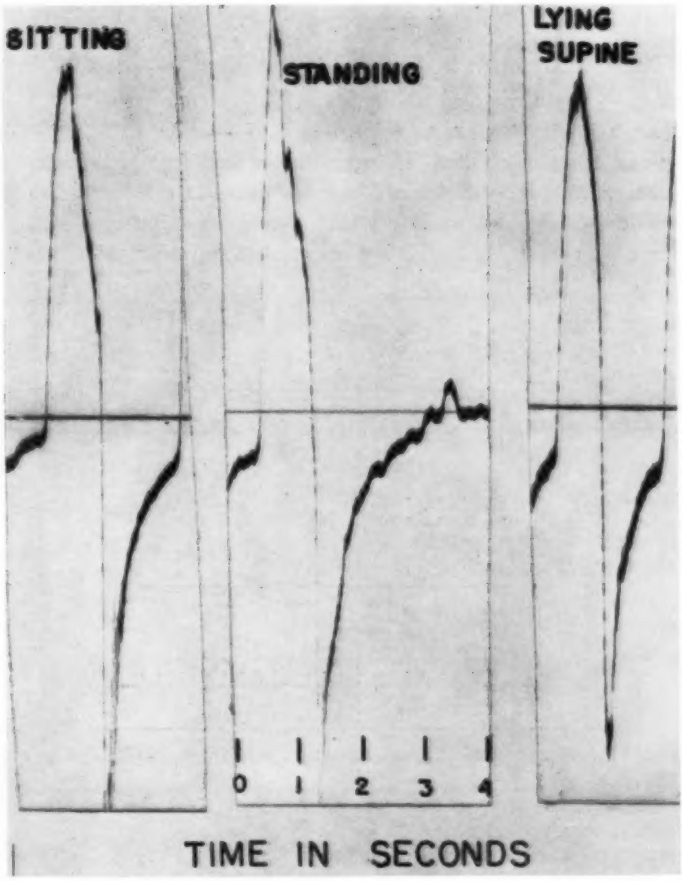


FIG. 16. Maximum effort pneumotachogram on a normal subject in positions indicated.

patients with extensive bronchiectasis and, since alveolar pressures were only about twice normal, tissue viscance probably played a large part in this disability (see above in section on forces impeding air flow). This patient's maximum breathing capacity was 36 liters per minute, (ventilatory reserve 80 per cent).

2. Five patients had maximum effort pneumotachograms demonstrating prolonged inspiratory effort with low flow velocity. Such a pattern is shown in figure 17B. Some of the patients have a much prolonged expiratory effort, (fig. 18 A&B). In one patient (A.V.A.), although 1390 ccs. could be inspired in 0.65 seconds, 1.35 seconds was required to complete the following expiration. This patient had extensive pulmonary tuberculosis and a unilateral pneumothorax. His maximum breathing capacity was 78 liters per minute, (ventilatory reserve 92 per cent). In the normal subject during maximum effort,

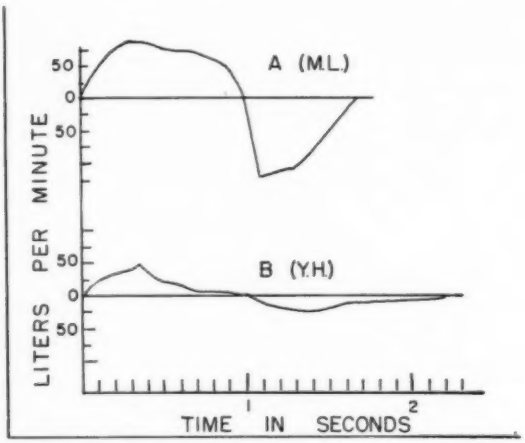


FIG. 17A. Maximum effort pneumotachogram on a patient (M.L.) with multilobar bronchiectasis.

B. Maximum effort pneumotachogram on a patient (Y.H) with multilobar bronchiectasis.

almost exactly the same amount of time is required for expiration as for inspiration. Another patient (C.B.) inspired 387 ccs. in 0.6 seconds but 1.65 seconds was required for the ensuing expiration. This patient had a marked degree of pulmonary emphysema and a maximum breathing capacity of 31 liters per minute, (ventilatory reserve 68 per cent). In neither of these patients could the prolonged expiration be explained by a differential between inspiratory and expiratory alveolar pressure. Twenty-two patients, or almost half of those studied, required a disproportionate amount of time to expel air during maximum effort.

3. In those patients who were dyspneic at rest maximum effort produced little change in the respiratory pattern. Increase in volume of ventilation in these patients is accomplished largely by increasing the respiratory rate (fig. 19A&B).

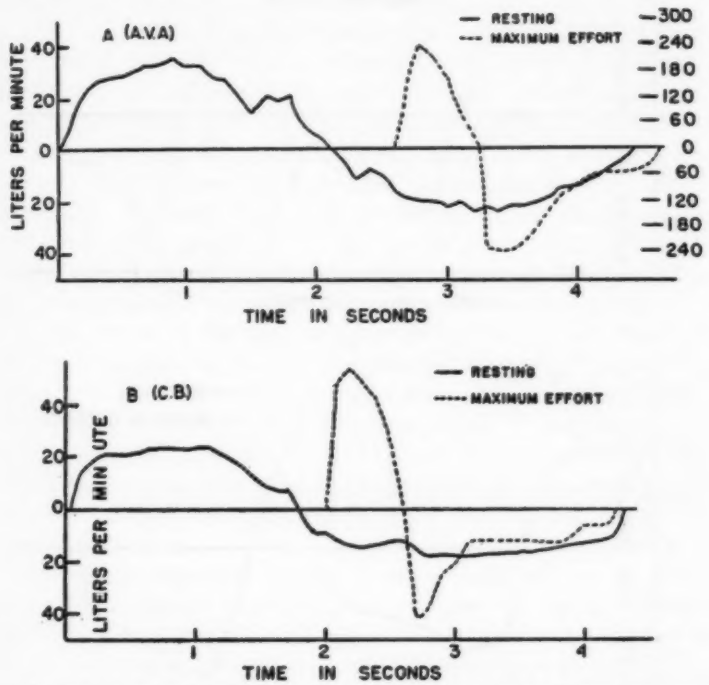


FIG. 18A. A, V. A., Patient with pulmonary tuberculosis, unilateral pneumothorax.

B, C. B., Patient with pulmonary emphysema.

In general the reduction in a patient's ventilatory reserve may be said to be due to:

A. Increase of the work of breathing at relatively high flow velocities owing to: the resistance due to the turbulence in pulmonary air flow, increased tissue viscance in the lungs, and loss of lung elasticity. Increase in the resistance to air flow offered by the respiratory tract does not appear to be a major factor.

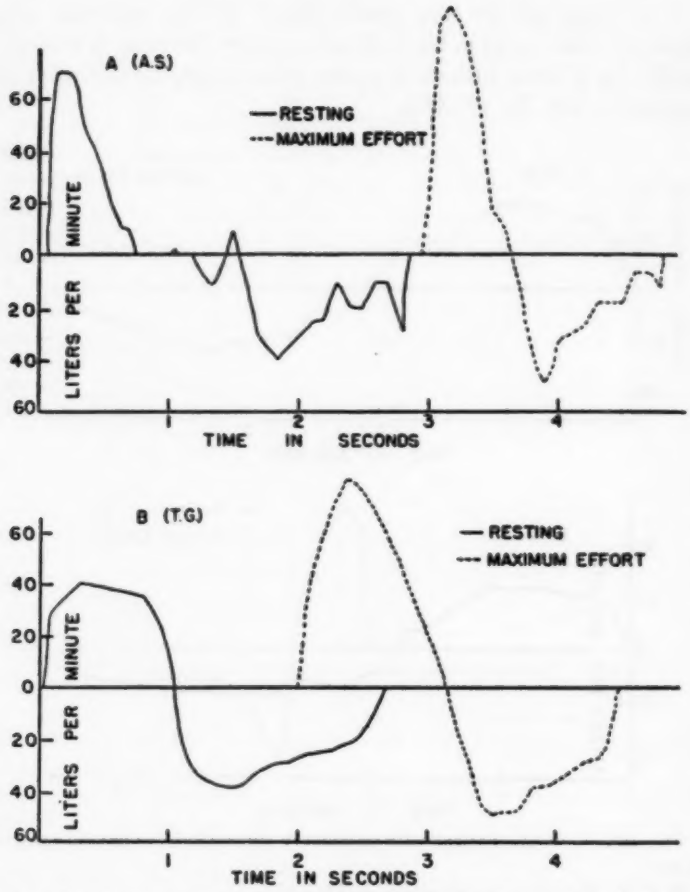


FIG. 19A. A. S., A patient with severe bronchial asthma and bronchiectasis and marked dyspnea at rest.

B. T. G., A patient with emphysema and pulmonary fibrosis with moderate dyspnea at rest.

B. The necessity to increase resting ventilation to maintain resting respiratory function.

DISCUSSION

The alterations in ventilatory function associated with various kinds of pulmonary disease may be considered by dividing the patients into four groups, those with, 1. loss of lung tissue, 2. loss of lung elasticity, 3. increased resistance to air flow, and 4. increased tissue viscance.

1. It is well known that more than half of a patient's lung tissue can be removed surgically without embarrassing respiratory function. Patients operated on because of lung tumors and bronchiectasis have repeatedly demonstrated the capacity to lead a normal existence. Ten of the patients in this series had undergone partial pulmonary resections. In none of these has evidence of serious respiratory deficiencies developed, nor have marked abnormalities in breathing patterns, alveolar pressure gradients, or lung volume relationships been found beyond those present prior to surgery and attributed to the underlying pulmonary disease. The same situation seemed to exist in some of the patients with bronchiectasis or tuberculosis who had not been submitted to surgery. At least in some instances loss of functioning lung owing to disease does not affect deleteriously the overall respiratory function measured by the technics employed in this study. Such patients have disease characterized by well defined localization (generally involving no more than 3 pulmonary lobes) in contrast to those patients suffering from pathological conditions with more diffuse distribution.

One patient, typifying this group, was a young woman, 26 years of age, with pulmonary tuberculosis. At the time she was studied there was a large cavity in the right upper lobe, disease at the apex of the left lung, and a pneumothorax on the left side. Her pneumotachogram is shown in figure 20. The pattern is similar to that found in the majority of normal subjects, as is also the maximum effort pneumotachogram. The alveolar pressure gradient was normal, vital capacity was 2,943 ccs. inspiratory reserve was 2,060 ccs., and expiratory reserve was 433 ccs. Minute volume was 6,540 ccs., and maximum breathing capacity 71 liters per minute, (ventilatory reserve 91 per cent). Exercise tolerance and spirometric tracings were normal.

2. Considering the known facts about the elastic forces in respiration one may speculate upon a theory of the pathogenesis of pulmonary

emphysema. There is evidence that the normal resting position of the chest wall, (when not opposed by the force of lung elasticity) corresponds to a lung volume of about 70 per cent of the vital capacity (8, 16, 17). In persons with severe emphysema in whom a large degree of lung elasticity has been lost, the resting respiratory position is approximately at this volume (18, 19). This would indicate that in such patients the tendency of the thoracic cage to rest at this position persists when lung elasticity is lost. Whether under such circumstances, this tendency can be properly called an elastic force is of little importance. The fact seems to be that in the normal subject, as well as in

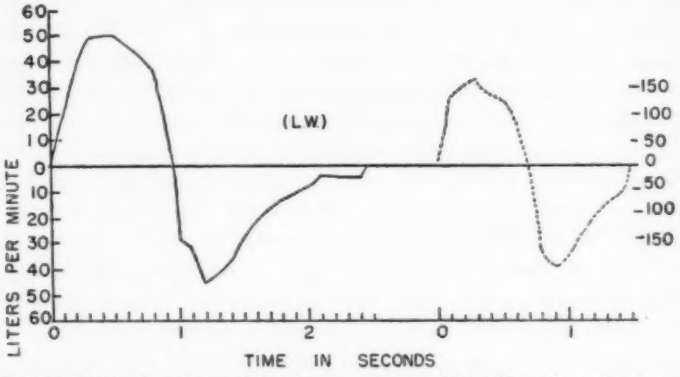


FIG. 20. L. W., A patient with pulmonary tuberculosis bilateral, cavitation and pneumothorax. Dotted line shows maximum effort.

the patient who has lost lung elasticity, the chest wall not only resists motion in either direction from this point but tends to return to this point when the force moving it has been removed. If a person were to gradually lose pulmonary elasticity without a corresponding loss of chest elasticity there would be a gradual change in the resting point of the chest. As the force of lung elasticity is reduced, the resting point (where the opposing elastic forces are equal) will occur at higher and higher degrees of lung inflation. The end point of this change would be reached with about 100 per cent increase in alveolar volume. There would be no corresponding increase in the number of bronchioles nor, in all probability, in the cumulative cross sectional area of airways

leading to this volume (20). Thus there would be two important changes in the relationship of the alveolar volume to the bronchial tree: an alteration in the size of the alveoli relative to the cross sectional area of the tubes allowing inflow of air, and a lack of the normal elastic concentric contraction of the alveolus when exposed to an increase in the pressure applied from without. Under this changed relationship when the intra-alveolar pressure is raised above the intra-bronchial pressure at the onset of expiration a greater proportion of the forces engendered may be exerted on surrounding structures, including the bronchi and blood vessels. The major effect of this would be greater constriction within the lungs of all the conducting pulmonary airways during expiration than is seen under normal conditions and a corresponding increase in resistance to expiratory airflow.

Although this hypothesis is largely based on simple conjecture and a priori reasoning there are facts to support it.

When a tracheotomy is performed on a patient in whom emphysema has developed because of severe tracheal or laryngeal obstruction the apices of the lungs are seen to bulge well into the neck and even cross each other at the midline with each expiratory effort. When the neck and chest are closed the force which produces this bulging (which exists throughout the lungs) acts on all the structures contained in the thoracic cage, including the airways, the heart and blood vessels. Emphysema develops in such a person as a result of the resistance to respiratory air flow (which in this instance is equal in expiration and inspiration). Expiration being ordinarily a less forceful and more passive procedure than inspiration, there is a tendency under these circumstances for the resting point to shift towards a greater degree of lung inflation. This has been demonstrated spirometrically in normal subjects breathing against added resistance (fig. 8B). It is also nicely demonstrated when there is a foreign body in the bronchus. The so called check valve mechanism, frequently offered as the explanation for this phenomenon, probably occurs only rarely. A foreign body in the bronchus offering the same resistance to expiration as to inspiration can result in emphysema in the lung beyond it, sometimes severe enough to cause partial collapse of the other lung. An example would be a bead filling the bronchial lumen but with its perforation in the line of air flow.

Of 8 patients with pulmonary emphysema 2 showed definitely higher expiratory alveolar pressure gradients than inspiratory; 5 others showed a questionable difference and in 1 there was no difference. Of 6 asthmatic patients 3 showed higher pressures, and 3 no difference.

In some patients there is probably enough change in the substance of the lung through fibrosis and scarring to interfere with the transmission of the intra-alveolar force to the bronchial walls. One of the authors has frequently observed bronchoscopically in emphysematous and asthmatic patients collapse of bronchial walls during expiration, most marked on coughing, by contrast in patients with long standing emphysema such a bronchial collapse is not always observed. In such patients prolonged expiration would have to be explained on a basis of ineffective use of the expiratory muscles and lack of the helping force of elasticity, chest elasticity opposing expiration and lung elasticity being absent.

One may wonder why the normal subject does not encounter resistance to an expiration after a maximum inspiration. This might be explained by the way in which elastic forces in the normal lung are exerted upon the alveoli even at maximum inflation in contrast to the absence of such forces in the emphysematous lung.

3. In addition to the above, increased resistance to air flow could arise from tumor masses or foreign bodies, thickened bronchial mucous membrane or viscid secretions lining the bronchial walls. The fact that patients with severe suppurative pulmonary disease show only moderate resistance to air flow probably indicates that where these factors are most prominent the lung beyond plays little part in the ventilatory process. It seems reasonable to conclude that resistance to air flow in pulmonary disease is of great importance, only when: A, it amounts to complete obstruction and results in atelectasis; B, it produces very severe resistance or resistance more marked during expiration leading to emphysema; or C, when it is of such a nature as to cause turbulence in air flow thus limiting the patient's ability to produce high flow velocities. The latter may be especially true when thickened mucous membrane alters the nature of the bronchial spurs from their usual sharp front to a rounded or irregular contour.

4. The evidence from these studies indicates that increase in tissue viscance may play an important part in respiratory changes in pul-

monary disease. Since studies have indicated that in the normal individual only 15 per cent of the work of breathing is expended upon tissue viscance while 22 per cent is expended on opposing air viscance and 63 per cent on elastic forces, it is apparent that any increase in the proportion of work expended on tissue viscance might alter respiratory activity. This alteration would be especially noticable when the proportion of work expended upon elastic forces is reduced. The full significance of such an alteration has not been explored and it is likely that suitable animal experiments will be necessary to gain the desired information on this subject.

It has been known for some time that proper use of therapeutic respiratory exercises can increase the patient's comfort at rest and his ventilatory reserve. From these studies it is easy to understand how properly directed respiratory training may make such a difference. One would expect that this training might be most fruitfully aimed at the development of a more efficient use of respiratory musculature in expiration in those patients with loss of lung elasticity, and a proper adjustment of respiratory timing especially attempting to correct unnecessarily prolonged expiration.

It is also conceivable that if patients with severe emphysema due to loss of lung elasticity could be discovered before the process has become irreversible they might be trained to hold the mid-point of breathing at a lower level and arrest the progress of this disease.

Attempts have been made to discover some quantitative methods of analysing the pneumotachogram which might simplify its interpretation and allow one to draw more exact conclusions from the variations in pattern which have been observed. So far these attempts have not met with any obvious success. As suggested in the first article of this series this may be attributable to lack of sufficiently large numbers of normal subjects and of patients with pulmonary disease; or, some of the apparent confusion may be due to the inclusion among the normal subjects of those who have respiratory abnormalities not at present determinable. Some of the quantitative measurements now being studied are tabulated in figure 21. Because of the small number of patients in each category of pulmonary disease it is impossible in most instances to draw any conclusions as to the relationships between any particular type of disease and those measurements. There does appear

to be some significant difference between the patients and the normals as shown in the relationship between maximum velocities and resting velocities, between respiratory cycle time and inspiratory time during

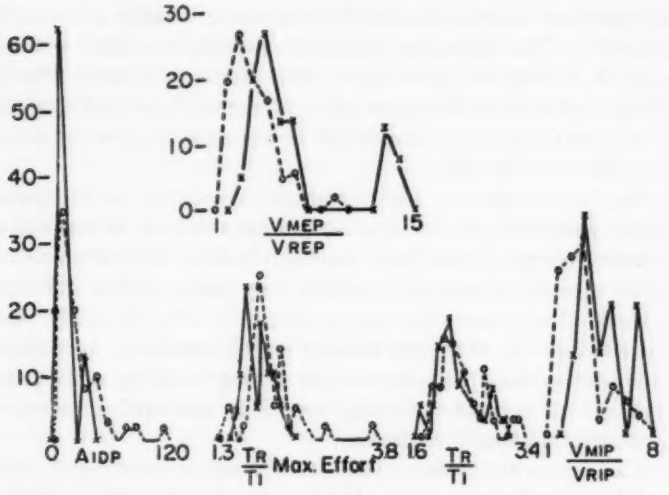


FIG. 21. Analysis of the pneumotachogram: The statistical significance of the difference is difficult to estimate until larger numbers of both patients and normals are studied. Represented on the chart from left to right below: the initial acceleration at the beginning of inspiration expressed in ccs. per (0.1 sec.)^2; respiratory cycle time divided by inspiratory time during maximum voluntary effort; respiratory cycle time divided by the inspiratory time in the resting state; inspiratory peak velocity during maximum voluntary effort divided by inspiratory peak at rest; and above, expiratory peak velocity during maximum voluntary effort divided by resting expiratory peak. In each instance the range of values is indicated by the first and last numbers on the abcissae on each chart. The figures on the ordinates indicate percentage of subjects. On the first and third charts 17 normal subjects and 47 patients are represented, in the remaining charts 15 normal subjects and 40 patients are represented. The dotted lines represent patients and the solid lines represent normal subjects.

maximum effort, and the acceleration at the onset of inspiration (A_{IDP}).

No method has yet been found of quantitatively expressing the

obvious differences between some of the patients and the normals. This is especially true of the character of the deceleration A_{EPI} and the position of and relative predominance of the peaks V_{DP} and V_{CP}. Different and better methods of quantitative analysis are continually being sought and when found should facilitate a more clear cut differentiation between the normal and abnormal and the various phases of abnormality.

SUMMARY

Part 1 (Article 1 of this series)

1. Experimental analysis of normal pneumotachograms has substantiated the hypothesis that portions of the respiratory pattern are true reflections of the activity of the respiratory musculature, the effectiveness of lung elasticity, and the manner in which reversal of respiratory effort is accomplished.

2. Study of records taken during maximum respiratory effort provides information facilitating a classification of the factors controlling ventilatory reserve: the ability to reach high velocities, the time during which such high velocities can be maintained, and the time required for reversal of direction of flow of air.

3. The pneumotachogram yields information about the manner in which the organism adapts the respiratory apparatus to added resistance to breathing, especially when combined with studies of the alveolar atmosphere pressure gradient.

Part 2

4. Indications of abnormalities in lung elasticity may be discovered by study of the pneumotachogram—especially in patients with pulmonary emphysema or fibrosis.

5. There is evidence that bronchial resistance to air flow plays a relatively small role in alterations of the pneumotachogram in patients with pulmonary disease. Increased tissue viscance is probably largely responsible for the "resistance" type of pattern.

6. The limitation in ventilatory reserve so often found in patients with pulmonary disease may be studied in detail by air flow velocity measurements. Such studies may be used to aid in the direction of

respiratory exercises. Turbulent air flow developing at relatively low flow velocities seems to be an important factor in the reduction of ventilatory reserve.

BIBLIOGRAPHY

1. Proctor, D. F., and Hardy, J. B., Studies in Respiratory Air Flow, 1. The Normal Pneumotachogram, Bull. Johns Hopkins Hosp., Vol. 85: 253–280, 1949.
2. Carson, On the Elasticity of the Lungs., Phil. Trans. Roy. Soc. London, **1820:** 110, 29.
3. Heynsius, Über die Grosse des Negativen Drucks im Thorax beim ruhigen Athmen. Arch. f.d. ges. Physiol. **1882:** 29, 265.
4. Rohrer, F., Physiologie der Atembewegung. Handbuch der Normalen und Pathlogischen Physiologie, Zweiter Band, 70–127, 1925.
5. Neergaard, K. v., and Wirz, K., Über eine Methode zur Messung der Lungen elastizität am lebenden Menschen, insbesondere beim Emphysem. Ztchr. f. Klin. Med. **105:** 35–50, 1927.
6. Fleisch, A., Der Pneumotachograph; ein Apparat zur Geschwindigkeitsregistrierung der Atemluft. Pflugers Arch. f.d. ges. Physiol. **209:** 713–722, 1925.
7. Vuilleumier, P., La Signification de la depression pleurale. Schweiz. Med. Wschr. **69:** 697–700, 1939.
8. Rahn, G., Otis, A. B., Chadwick, L. E., and Fenn, W. O., The Pressure Volume Diagram of the Thorax and Lung. Am. J. Physiol., **146:** 161–178, 1946.
9. Christie, R. V., The Elastic Properties of the Emphysematous Lung and their Significance. J. Cl. Invest. **13:** 295–321, 1934.
10. Otis, Proctor, Rahn, Measurement of Alveolar Pressure and Work of Breathing. Federation Proc., **152:** 106–112, 1948.
11. Personal Communication from Dr. A. B. Otis, Department of Physiology, University of Rochester, N. Y. December 1949.
12. Vuilleumier, P., Über eine methode zur Messung des Intraaveolären Drucks und der Strömungswiderstände in den Atembewegen des Menschen., Zeits. Klin. Med., **143:** 698, 1944.
13. Otis, A. B., Proctor, D. F., Measurement of Alveolar Pressure in Human Subjects. Am. J. Physiol., **152:** 106–112, 1948.
14. Otis, A. B., and Bembower, W. C., The Effect of Gas Density on Resistance to Respiratory Gas flow in Humans, in press, Jour. of Applied Physiol.
15. Prandtl and Tietjens, Applied Hydro and Aeromechanics, McGraw Hill Book Co., Inc., 1934.
16. Gerhardt, D., Über den Druck im Pleuraexudaten. Arch. f. exper. Path. und Pharmak. Suppl. 1908, 228–234
17. Banta, E., The Relation of Intrapleural Pressure and Pulmonary Collapse in Artificial Pneumothorax. Am. Rev. Tuberc. **33:** 203–214, 1936.

18. CHRISTIE, R. V., AND MCINTOSH, C. A., The Measurement of Intrapleural Pressure in Man and its Significance, J. Clin. Invest. **13:** 279–294, 1934.
19. HURTADO, A., KALTREIDER, N. L., FRAY, W. W., BROOKS, W. B., AND MCCANN, W. S. Studies of Total Pulmonary Capacity and its Subdivisions. V. Observations on Cases of Obstructive Pulmonary Emphysema, J. Clin. Invest. **13:** 1027–1051, 1934.
20. NICHOLSON, H. C., AND TRIMBY, R. H., An Attempt to Detect Reflex Changes in Bronchial Calibre Synchronous with Respiration. Am. J. Physiol., **128:** 276–280, 1940.

A UNIQUE CASE OF OBSTRUCTION OF THE INFERIOR VENA CAVA

IVAN L. BENNETT, JR.

The Department of Pathology, The Johns Hopkins University School of Medicine

Received for publication June 23, 1950

Obstruction of the inferior vena cava is not uncommon. The last complete review of this condition was that of Pleasants (1), who in 1911 was able to collect 296 instances from the literature to which he added 18 cases from the records of the Johns Hopkins Hospital. In the ensuing 40 years numerous additional cases have been reported.

By far the commonest type of obstruction is that due to thrombosis, usually the result of extension from the iliac veins of a process initiated in the lower extremities. Thrombus formation is likewise often a final event in instances of partial obstruction by invading tumors or external compression, either inflammatory or neoplastic. Other causes of occlusion of this vessel are congenital malformations and surgical ligations.

The present case is presented because of the long clinical course as a puzzling diagnostic problem and the unusual type of obstructive process found at autopsy.

CASE REPORT

E. L., a 66 year old colored male, was admitted to the medical service of the Johns Hopkins Hospital (History No. 121106) for the fifth time on February 9, 1950 because of increasing weakness and progressive signs of liver failure. He had a long and complex history of illness.

His first admission to the hospital was in December, 1937. He had been in good health until 1935 when, at the age of 51, he noted the gradual onset of post-prandial gaseous distension, constipation and weakness. With progression of these symptoms there developed anorexia, occasional nausea, and weight loss of about 16 pounds over a two year period. The salient features of physical examination at this time were low-grade fever, evidence of weight loss, hepatomegaly, and ankle edema. The spleen was not felt. At the time of admission, one observer commented on the fact that the lateral thoracic veins seemed somewhat prominent. Laboratory studies revealed normal red cells and hemoglobin, mild albuminuria with normal PSP excretion, and some liver dysfunction as evidenced by 60% retention of BSP and decreased galactose tolerance. There was no icterus; the blood serological

test for syphilis was negative. Extensive X-ray studies of the gastrointestinal tract, chest, skeleton, and urinary tract failed to reveal any evidence of malignant disease. The patient showed increasing edema of the lower extremities and developed ascites during the first three weeks of hospitalization; most observers came to feel that the diagnosis of Laennec's cirrhosis was the most likely one. Because of increasing prominence of the superficial veins of the lateral abdomen, venous pressure studies were done which revealed normal levels in the upper extremities but pressures in the femoral veins were consistently above 300 ml of saline solution. The possibility of obstruction of the inferior vena cava was entertained and an exploratory laparotomy was performed on January 3, 1938. No evidence of any obstructing lesion of the vena cava below the diaphragm was found. The liver was large with slightly granular surface; the spleen was normal in size. An omentopexy was performed and a liver biopsy was obtained. This was interpreted as showing chronic passive congestion and early scarring, probably central in distribution.

The patient was discharged in May, 1938 after gradual improvement on bed rest and diuretics but was readmitted with a recurrence of massive ascites and edema six weeks later. On this admission, gynecomastia and hemorrhoids were noted. Because of the possibility that a localized constrictive pericarditis involving the inferior vena cava as it entered the right atrium might be the source of difficulty, a thoracotomy was performed on June 26, 1938 and the pericardium was found to be entirely normal. There was no evidence of any thrombosis of the thoracic segment of the inferior vena cava.

The patient was seen in the outpatient department on numerous occasions during the next few years. His condition remained relatively enchanged, the edema yielding fairly well to diuretics. He steadily refused to remain upon the diet prescribed and was known on several occasions to take large quantities of alcohol. He was admitted in April, 1946 for treatment of cellulitis of the lower extremities; this infection yielded promptly to penicillin and heat. At this time, the serum albumin was 3.9 gm and the serum globulin 4.5 gm. There was decreased galactose tolerance, decreased excretion of hippuric acid and 60% retention of BSP. For the first time, esophageal varices were demonstrable by X-ray.

In August, 1949, he was readmitted with a two weeks history of malaise, melena, hematemesis, and jaundice, complicated by the development of lobar pneumonia. Red blood count on admission was 2.3 million, hemoglobin was 7.5 gm, and hematocrit was 27%. Other laboratory studies showed: icterus index 55, bilirubin 7.4 mgm, alkaline phosphatase 3.3 Bodansky units, serum albumin 2.9 gm, serum globulin 5.1 gm, cephalin flocculation 2+, and thymol turbidity 13.5 units. After receiving transfusions and penicillin, the patient improved once more.

During the next few months he became progressively more jaundiced and weaker until his final admission on February 9, 1950 when he was edematous, icteric, and semicomatose. Laboratory studies revealed anemia, and a prothrombin concentration of only 45%. He responded poorly to treatment, lapsed into coma, and died three days later on February 12, 1950. The final clinical impression was:

obstruction to inferior vena cava, etiology undetermined, with cirrhosis and venous varicosities.

Autopsy was performed 26 hours after death. The body was that of an elderly

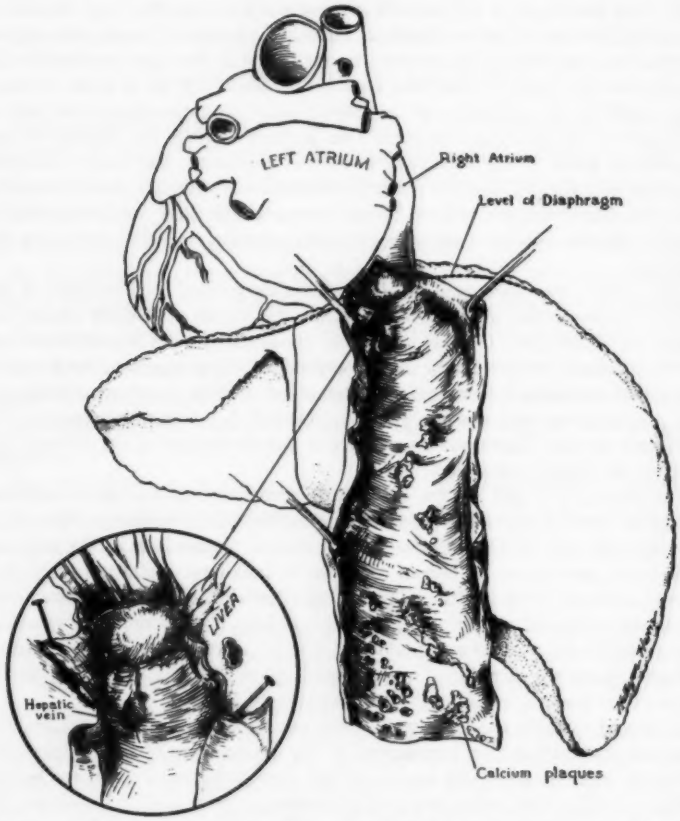


FIG. 1. Sketch showing location of membranous obstruction in inferior vena cava.

colored male weighing 83.5 kg and measuring 181 cm in length. There was scleral icterus and a right conjunctival hematoma. The skin of the lower legs was hyperpigmented, indurated and wrinkled. The scrotum was large and edematous; bilateral hydrocele was present. The abdomen was protuberant; the veins of the

lateral abdominal walls, especially the right, were tremendous, tortuous, and dilated, extending to lower thoracic collaterals. Well-healed right upper abdominal and left thoracic operative scars were present. The axillae contained no hair and the pubic hair was scanty; there was bilateral gynecomastia.

The *abdominal cavity* contained about 500 ml of icteric, clear, non-clotting fluid. The atrophic omentum was adherent to the abdominal scar.

The *heart* weighed 350 gm and except for flabbiness of the myocardium was normal throughout, including the coronary arteries. The parietal pericardium was adherent to the epicardium by easily broken fibrous adhesions.

There was no pleural fluid. The *lungs* were sodden and heavy; on cut surface they were edematous and the lower lobes suggested terminal aspiration.

The *liver* weighed 1700 gm and showed marked cirrhosis with nodules up to 5 mm in diameter separated by fibrous tissue strands. The organ cut with increased resistance; the liver parenchyma was light yellow. The gall bladder and extrahepatic biliary ducts were normal throughout.

The *spleen* weighed 280 gm; its capsule showed yellowish, nodular thickenings. The hilar vessels were normal and cut surface showed only congestion.

The *esophagus* contained several superficial erosions in its upper portion, and near the cardia its wall contained numerous tortuous, dilated veins. There were many varicose veins in the *rectum*.

The *adrenals* were quite small; the left weighed 3.2 gm and the right 2.9 gm. Except for depletion of cortical lipoid, their cut surfaces were not abnormal.

There was bilateral hydrocele and both spermatic cords contained large varicosities. The *testes* were small and atrophic. The right measured 3.5 x 1.5 cm and the left 4.0 x 2.0 cm.

The *aorta* was elastic throughout, containing one atherosclerotic plaque just below the origin of the renal vessels. Although the *splenic vein* was delicate, the *portal* and *superior mesenteric veins* were dilated and the wall of the portal seemed thickened. No valves or other abnormalities were seen in these veins. The *azygos vein* was not particularly prominent. The *superior vena cava* entered the right atrium normally. The *inferior vena cava* was found to be completely obstructed at the level of the diaphragm by a fibrous membrane 4 mm in thickness. There was very slight constriction at this point of obstruction. The portion of the vessel above the diaphragm was delicate, measured 5 cm in length, and received no tributaries. The portion of the inferior vena cava below the diaphragm was thick-walled and dilated, its walls as far down as the iliacs containing numerous atherosclerotic and calcific plaques. The *hepatic veins* were thick-walled and dilated, but the *renal veins* were both delicate. There was marked dilatation of the small branches of the *iliac* and *femoral veins* including the *external pudendals* and the *circumflex iliac veins*.

Microscopically, sections of *heart*, *gall bladder*, *pancreas*, *kidneys*, *thyroid*, *parathyroids*, axillary, inguinal and mediastinal *lymph nodes*, *hypophysis*, *brain*, and *bone-marrow* were normal.

All sections of *lung* showed patchy alveolar hemorrhage and pulmonary edema.

The *liver* was of great interest, showing what seemed to be a combination of two distinct processes. There was a typical Laennec's cirrhosis, with relatively delicate scars and nodules of regenerating or remaining hepatic cells many of which were extremely distended with fat. Superimposed on this picture, there was noted a system of broader, more irregular and more vascular scars, containing no bile ducts. Due to lobular collapse, these scars were sometimes contiguous to the periportal regions but many clearly had their origin about central or hepatic veins. The whole picture was consistent with a combination of portal and chronic passive congestion cirrhosis.

Sections of *spleen* showed congestion only. Numerous dilated veins beneath the esophageal mucosa and in the rectum were the only findings of interest in the gastrointestinal tract.

Both *testes* were atrophic as was the *prostate* which contained only occasional islets of acinar tissue.

Both *adrenals* presented a similar picture, there being marked atrophy of a large part of the fasciculate and reticular zones, leaving the glomerulosa intact, and indeed, in an abundance strongly suggesting hyperplasia. Occasional nodules of fasciculate or reticular cells were present.

Sections of *breast* showed ductal hyperplasia.

Microscopically, the membrane occluding the inferior vena cava was seen to consist of dense, hyaline, fibrous tissue with endothelium covering both surfaces and containing several small foci of calcification. No old blood pigment was seen in the tissue and iron stains revealed no hemosiderin. Stains for elastic tissue showed that occasional strands of the elastica of the vein wall penetrated for a short distance into the membrane. Sections of the *inferior vena cava* below the obstruction showed increased fibrous tissue and muscle hypertrophy of its wall with atheromatous plaques containing calcium. The *hepatic veins* were thickened and showed muscle hypertrophy at their junction with the vena cava. The *portal vein* showed hypertrophy of its muscularis.

The final anatomical diagnosis was: *Complete obstruction of inferior vena cava (congenital malformation?) above the hepatic veins by fibrous diaphragm. Thickening and calcification of inferior vena cava below obstruction. Dilatation of superficial abdominal and lateral thoracic veins. Bilateral hydrocele and varicocele. History of alcoholism and inadequate diet. Combined portal and central cirrhosis of liver. Ascites. Edema of legs. Esophageal varices. Splenomegaly. Jaundice. Loss of axillary and pubic hair. Bilateral gynecomastia. Testicular atrophy. Atrophy of prostate. Bilateral focal atrophy of fasciculate and reticular zones of adrenals, with hyperplasia of glomerular zones and nodules of regeneration of other zones. Pulmonary edema and hemorrhage. Superficial erosions, esophagus. History of pericardiotomy and omentopexy. Fibrous adhesions, pericardium.*

DISCUSSION

The clinical signs and symptoms of obstruction of the inferior vena cava, which have been discussed in detail by Wakefield (2) and Hal-

lock, Watson, and Berman (3), require no repetition here. The embryology and anatomy of the inferior vena cava and its collateral channels are described by Gladstone (4) and in the monograph by McClure and Huntington (5).

A careful search of the literature has failed to reveal another example of membranous closure of the inferior vena cava at this site. It seems unlikely that the obstruction in the present case was the result of thrombosis. While absence of any microscopic iron pigment is not incompatible with an organized thrombotic process of several years duration, the location of the fibrous diaphragm and its thinness argue strongly against a role of thrombosis in its origin. Nor was there any evidence whatever that the membrane resulted from an extramural inflammatory process or other encroaching lesion. Its location was not such that it can be considered to have resulted from an improper fusion of the anterior two of the three embryologic segments of the inferior vena cava, nor could it conceivably have resulted from the absence of one of them

It is to be emphasized that the liver presented the characteristics of portal cirrhosis of the Laennec type, a finding which cannot be attributed to increased hepatic venous pressure alone. Could this have been a congenital obstruction, present since birth as a "coarctation" of the inferior vena cava? The fact that the onset of symptoms and appearance of clinical signs was delayed until the age of 51 might seem to be strong argument against such a proposal, but a review of some of the reported cases of congenital obstruction of the inferior vena cava removes that objection.

Osler (6) reported the case of a 24 year old man who had had mild pedal edema for about five years and who suddenly developed ascites and superficial abdominal vein distension during the last two months of life. Autopsy showed that the segment of the inferior vena cava between the renal veins and the hepatic veins was completely obliterated, remaining only as a dense fibrous cord about six cm in length and one cm in diameter. No evidence of old blood clot was seen microscopically and Osler postulated that the obstruction was congenital. The liver showed a type of cirrhosis; according to Osler's notes, the scars were peripherally placed in the lobules. While others have disagreed that this case represented a congenital defect (7), the obstruction, whatever its etiology, had obviously been present for more than

the short period during which collateral circulation had been noticeable. Whether the cirrhosis was actually portal in type is now only a matter for conjecture, but the possibility that the development of a complicating cirrhosis was responsible for the relatively sudden and late appearance of obstructive signs remains.

Cavasse (8), in 1897, reported findings in a 54 year old white male dying of pneumonia who for two years had shown distension of the veins of the lateral abdominal walls and in whom a clinical diagnosis of vena caval obstruction had been made. At autopsy, the inferior vena cava was found to end abruptly below the renal veins without even a fibrous cord connecting it to the iliacs. The right spermatic vein via the pudendal plexus and its interconnections with the epigastrics formed the main collateral channel. That this was an arrest of the development of the lower posterior cardinal system seems undeniable and yet, superficial collateral channels appeared only at the age of 52 years. There was no cirrhosis.

Meyer (9) observed an 18 year old male who died of erysipelas after only two months of an illness characterized by pedal edema, ascites, and the rapid development of abdominal collaterals. Autopsy revealed obliteration of the inferior vena cava at about the level of the diaphragm for a distance of one cm with marked constriction. The hepatic veins in this case were described as dilated but whether they entered the vena cava above or below the obstruction is not stated and is not shown in the sketch accompanying the case report. There was no cirrhosis. Lacking evidence for any other etiology, Meyer suggested that this obstruction might have been congenital. Whether congenital or not, it was obviously of much longer standing than the two months during which symptoms and signs had been present. Commenting on the late appearance of superficial collaterals in vena caval obstruction, Meyer mentions the case of Andrews (10), a 35 year old woman dead of cancer in whom complete obstruction of the vena cava by a fibrous plug just below the renal veins was found. She had never had any enlargement of the superficial veins. Bloch (11) described a similar instance of cicatricial obstruction below the renal veins without signs or symptoms. The failure of development of superficial collateral channels in cases of obstruction below the renal veins is not surprising in view of the paucity of findings in patients in whom surgical ligation has been performed at this site (12).

Griffith (13) found complete closure of the inferior vena cava above the renal veins in a 55 year old man without superficial venous enlargement or ascites. Keen (14) describes in detail a case in which the vena cava between the renal and hepatic veins remained only as a fibrous cord in a man 71 years old who died suddenly from other causes. Although there had been no signs of collateral circulation during life and the condition was entirely unsuspected, extensive deep collaterals were present.

MacCallum (15) described the findings in a 28 year old man who died of lobar pneumonia in whom, without any evidence of embarrassment of the caval flow, the segment of inferior vena cava between the renal and hepatic veins was a fibrous cord, most of the caval flow passing either to the portal vein via collaterals or to the superior vena cava via the enlarged azygos.

Of interest as an example of "silent" obstruction of the vena cava showing signs only when some complicating disease develops as the case of a 33 year old woman reported by Sparks and Fox (16). This patient presented the signs of edema, ascites and impaired liver function with a steady downhill course. The total duration of the illness was 18 months. At autopsy, a typical Laennec's cirrhosis was found and, in addition, the inferior vena cava from the iliacs to the hepatic veins was a solid fibrous cord. Only mild evidence of superficial collaterals was present during life, persistently high femoral venous pressures being the only clue to the obstruction. The authors pointed out that no pronounced evidence of obstruction appeared until the development of portal cirrhosis with superimposition of portal obstruction upon the long-standing caval block.

SUMMARY

The present case is presented as one in which the signs of obstruction of the inferior vena cava were definitely present for 12 years in a man who died at the age of 66. Autopsy showed a thin fibrous membrane completely obstructing the vessel just above the entrance of the hepatic veins. In the absence of evidence for any other etiology and because of its membranous nature, it seems probable that this obstruction was congenital, the late onset of signs and symptoms resulting from the development of a complicating Laennec's cirrhosis and portal hypertension. Previously reported instances of long-stand-

ing vena caval obstruction with late development of clinical signs are cited in support of this thesis.

REFERENCES

1. Pleasants, J. H.: Obstruction of the inferior vena cava with a report of eighteen cases. Johns Hopkins Hosp. Reports, **16:** 363, 1911.
2. Wakefield, E. G.: Obstruction of the inferior vena cava. Med. Clinics of N. America, **14:** 811, 1930.
3. Hallock, P., Watson, C. J., and Berman, L.: Primary tumor of inferior vena cava, with clinical features suggestive of Chiari's disease. Arch. Int. Med., **66:** 50, 1940.
4. Gladstone, R. J.: Development of the inferior vena cava in the light of recent research, with especial reference to certain abnormalities, and current descriptions of the ascending lumbar and azygos veins. Jour. of Anatomy, **64:** 70, 1929.
5. McClure, C. F. W. and Huntington, G. S.: The mammalian vena cava posterior. The American Anatomical Memoirs, #15, August, 1929.
6. Osler, W.: Case of obliteration of vena cava inferior, with great stenosis of orifices of hepatic veins. Jour. Anat. and Physiol., **13:** 291, 1878–79.
7. Huseby, R. A. and Boyden, E. A.: Absence of the hepatic portion of the inferior vena cava with bilateral retention of the supracardinal system. Anat. Record, **81:** 537, 1941.
8. Cavasse: Atrésie de la veine cava inférieure (arrêt de développement de la cardinale droite postérieure). Bull. de la Soc. Anat. de Paris, **11:** 811, 1897.
9. Meyer, A.: On a case of complete fibrous obstruction (congenital?) of both superior and inferior venae cavae in a young man of eighteen years—first recorded case Medical Record, **63:** 806, 1903.
10. Andrews: Transactions of Pathological Society. London, **16:** 92, 1864-65. Cited by Meyer (9).
11. Bloch: Über Obliteration der Vena Cava Inferior. Jena, 1880. Cited by Meyer (9).
12. Thebaut, B. R. and Ward, C. S.: Ligation of inferior vena cava in thromboembolism. Report of 36 cases, Surg., Gyn., and Obst., **84:** 385, 1947.
14. Griffith: Scalpel, London, **4:** 13, 1899. Cited by Pleasants (1) and Meyer (9).
14. Keen, J. A.: The collateral venous circulation in a case of thrombosis of the inferior vena cava, and its embryological interpretation. Brit. Jour. Surg., **29:** 105, 1941.
15. MacCallum, W. G.: Anomaly of the inferior vena cava with thrombosis. Studies from the Department of Pathology. College of Physicians and Surgeons, **13:** 1, 1913.
16. Sparks, A. L. and Fox, H.: Occlusion of the entire inferior vena cava. Arch. Path., **26:** 519, 1938.

A CLINICAL CLASSIFICATION OF VESTIBULAR DISORDERS

With Differentiation of Three Syndromes and Discussion of a Common Form of Vertigo Induced by Sudden Movement of the Head

F. R. FORD

Received for publication June 26, 1950

Vertigo is a very common and distressing symptom, but there is no general agreement about the interpretation of even the types which occur most frequently. It has occurred to me that something might be gained by separating vestibular disorders into three chief syndromes: 1. Symptoms due to spontaneous discharge. 2. Symptoms due to exaggeration of reflexes. 3. Symptoms due to loss of reflexes. Obviously many of the statements made below are well known and others are somewhat speculative.

I. Symptoms due to spontaneous discharge

(a)—First on the list we must place *Meniere's disease.* In this condition we find sudden, violent, spontaneous discharges of the vestibular mechanism which recur from time to time during a period of years. The symptoms are such as may be produced by strong stimulation of the vestibular apparatus by rapid rotation or by irrigation of the ear with large amounts of ice water. The onset is usually abrupt. There is vertigo with apparent rotation of the field of vision before the patient's eyes, nausea, vomiting, unsteadiness so that the patient cannot stand and, in severe attacks, shock which may be severe enough to cause syncope. The active phase of such attacks rarely lasts more than a few hours but the patient may feel the effects of the attack for several days. It is important to keep in mind that the vertigo develops spontaneously regardless of the patient's movements and that it is not relieved by lying still in a recumbent position. In between the attacks, there is rarely any disturbance of equilibrium. One finds of course, with very few exceptions, deafness and tinnitus in addition to the paroxysms of vertigo. An attack of vertigo is not, as a rule, followed by any great increase in the deafness. The deafness runs a

slowly progressive course with unpredictable fluctuations in severity. It is rare for total deafness to result. One or both ears may be affected. Crowe's paper (1) gives the most complete account of this disease.

Almost exactly the same clinical picture may be seen occasionally in cases of *chronic otitis* with or without cholesteatoma of the middle ear.

Rarely one may observe cases in which *focal cerebral discharges* (5) may give rise to symptoms suggestive of Meniere's disease. In such cases, the onset is even more abrupt but the vertigo is usually less severe and often very brief lasting in some instances only a few seconds. Frequently there are motor or sensory phenomena or disturbances of consciousness which suggest the proper diagnosis. Deafness and tinnitus are absent. Electro-encephalographic study is often helpful in the diagnosis. Anticonvulsive therapy may be effective.

(b)—In a somewhat different category we must place those attacks of vertigo which are associated with acute destructive processes involving the labyrinths or the eighth nerves. These, as a rule, show no tendency to recur. The onset is marked by vertigo, tinnitus, nystagmus and other evidences of vestibular irritation and the acute stage is followed by evidences of loss of vestibular function and deafness.

Inflammatory processes are most common. Here we place pyogenic labyrinthitis resulting from otitis or meningitis and lesions due to syphilis, mumps and herpes zoster. Vascular lesions in the labyrinth are rare but may occur as a result of arteriosclerosis, syphilis and leukemia. Various toxins have a similar effect. One may cite streptomycin, quinine and aspirin. Head injuries may result in hemorrhage in the labyrinth. An allergic labyrinthitis is described. More chronic processes such as acoustic neuromas are not likely to cause sudden vertigo.

During the active stages of these conditions we observe not only the symptoms of vestibular irritation, which I have termed the first syndrome, but also often an excessive response to movement of the head which constitutes our second syndrome, and is described below. After the active stage is over we may find evidences of loss of vestibular function which comprise the third syndrome.

The conditions mentioned above are most easily confused, in my opinion, with small vascular lesions in the brain stem, acute plaque

formation in the neuraxis in disseminated sclerosis or perhaps, bulbar encephalitis. In all of these we expect to find neurological signs of brain stem damage. Deafness may occur if the auditory mechanisms are involved.

II. Symptoms due to exaggeration of the vestibular reflexes

This is a very common condition which has not received the attention it should have and is frequently confused with Meniere's disease. It is characterized by vertigo on sudden movement of the head. The usual story is that arising from a recumbent position, lying down, turning the head to one side either in the upright or recumbent position, stooping and arising or looking upward will produce the vertigo. Quick movements are effective; slow movements cause less reaction. The vertigo is usually mild and brief, but may be violent. When lying still the patient is free of symptoms. I believe that the semicircular canals are stimulated by the sudden movements and the vertigo indicates an exaggeration of the normal reflexes.

During the acute stages of labyrinthitis, these reactions just described are usually present. In such instances the explanation seems to be clear. The labyrinth must be in a state of abnormal irritability.

The instances of this condition which are seen most commonly, however, are not at all easy to understand. Middle aged and elderly patients frequently complain of the symptoms mentioned above. In my experience, this is the commonest type of vertigo. Acute and severe attacks occur which may confine the patient to bed for several days. In other cases the symptoms are milder and the patient may continue an active life merely guarding himself against sudden movements. These milder symptoms may persist for weeks or months. They are as a rule at their worst when the patient first awakens in the morning and may pass off during the course of the day. They are usually inconstant. A certain movement may produce vertigo, but when repeated a short time later, may cause no reaction. There is no constant deafness but in many patients there is loss of high tones appropriate to the age. The vestibular reactions are brisk.

Many explanations have been offered for this condition such as arteriosclerosis, anemia, hypotension, debility and for the more severe and acute types, "serous labyrinthitis". The last is a purely theoretical

concept. Since, there is usually no deafness or loss of vestibular reactions, the use of the term labyrinthitis is open to criticism. The factor which has seemed to be most important in my experience of several hundred cases is prolonged nervous strain due to excessive responsibility, worry, anxiety and emotional instability. Since recovery almost invariably occurs with proper rest and relaxation, it is evident that arteriosclerosis is not entirely responsible. The physiological basis of this condition seems to be quite obscure.

It must be admitted that the tendency to this reaction increases with advancing age. Many elderly subjects are forced to guard their movements for this reason during their declining years. The condition seems to be constant in such cases. These patients are also unsteady on their feet even when standing still. It is conceivable that damage to central vestibular pathways may be responsible for some of the symptoms in elderly subjects.

Head injuries are not infrequently followed by dizziness of this type even when there is no apparent damage to the vestibular apparatus.

III. Symptoms due to loss of vestibular reflexes

Destruction of the vestibular apparatus on both sides in man produces a constant unsteadiness of station and gait which is exaggerated in the dark and also by sudden movements of the head. There is also a striking inability to fix objects with the eyes when the head is in movement so that the patients complain of objects seeming to dance or oscillate before their eyes when they are walking or riding in a car (2). This oscillation ceases as soon as the head is held still. These visual phenomena are due to the loss of vestibulo-ocular reflexes which influence the extraocular muscles in such a manner as to compensate for movements of the head. It is of interest that individuals who have lost their vestibular reflexes become disoriented under water and may drown since they may swim downwards in trying to rise to the surface (3).

This condition is observed in an incomplete form for a few months after sudden destruction of one labyrinth. Thereafter, a compensatory process results in disappearance of the symptoms. A gradual process resulting in destruction of one labyrinth does not cause such symptoms for compensation apparently develops parallel with the de-

struction. When both vestibular nerves are destroyed, the symptoms seem to persist for an indefinite time with little evidence of improvement.

The list of causes of this condition is a long one for any process which destroys the vestibular nerves or the labyrinths may produce it. Bilateral section of the vestibular nerves for Meniere's disease is, however, a good example. Excessive doses of streptomycin, syphilis of the eighth nerves and bilateral labyrinthitis due to meningitis may be mentioned. Some cases of congenital deafness display this syndrome and Levin (4) has reported a case in which a selective degeneration of the vestibular apparatus seemed to be responsible.

SUMMARY AND CONCLUSIONS

1. Disorders of the vestibular apparatus are separated into three chief syndromes. a—Those due to spontaneous discharge. b—Those due to increase of vestibular reflexes. c—Those due to loss of vestibular reflexes. These syndromes are described above. The otolith apparatus is not mentioned.

2. The first syndrome which is produced by spontaneous *discharge* is observed in an isolated form in Meniere's disease. The same symptoms may occur in acute processes involving the labyrinth or eighth nerve, such as labyrinthitis of various types, vascular disorders, intoxications, trauma and perhaps, allergic reactions. In such cases, the picture is complicated for a time by increase of reflexes and eventually by loss of reflexes.

3. The second syndrome, i.e. symptoms due to increase of vestibular reflexes, is seen not only in labyrinthitis and various types of vestibular irritation as mentioned above, but much more commonly in subjects of middle age who have been subjected to prolonged nervous strain. In such cases the symptoms are usually transient and there is no deafness or loss of function. This condition has been termed "postural vertigo," but since the vertigo is induced by movement of the head, might well be termed "movement vertigo." In elderly patients these symptoms are very common and apt to be persistent. Here it is possible we may be dealing with lesions involving the central vestibular pathways which are causing a *release* of vestibular reflexes.

4. The third syndrome, i.e. symptoms due to loss of vestibular

function, may result from any destructive process involving the vestibular apparatus whether this is acute or slowly progressive. When one labyrinth or eighth nerve is involved, the symptoms are usually of only a few months duration for *compensation* eventually occurs, but when both nerves are involved the symptoms are persistent. It is important to distinguish between discharge and loss of function so as to avoid useless operations.

REFERENCES

1. Crowe, S. J.: Meniere's disease. Study based on examination before and after intracranial division of the vestibular nerve. Medicine, **17:** 1, 1938.
2. Ford, F. R. and Walsh, F. B.: Clinical observations upon the importance of the vestibular reflexes in ocular movements. The effects of section of one or both eighth nerves. Bull. Johns Hopkins Hosp., **58:** 80, 1936.
3. James, W.: The sense of dizziness in deaf mutes. Amer. J. Otol., **4:** 239, 1882.
4. Levin, P. M.: The syndrome of vestibular paralysis in man. Jour. of Nerv. & Ment. Dis., **89:** 335, 1939.
5. Penfield, W. and Erickson, T. C.: Epilepsy and Cerebral Localization. C. C. Thomas, 1941 (page 105, vertiginous seizures).

THE DIFFERENTIATION BETWEEN EXTRAHEPATIC AND INTRAHEPATIC OBSTRUCTION OF THE PORTAL CIRCULATION

A Clinical Study of the "Banti Syndrome"*

OSCAR D. RATNOFF, C. LOCKARD CONLEY, and MORGAN BERTHRONG

Departments of Medicine and Pathology, The Johns Hopkins University School of Medicine

Received for publication July 5, 1950

In Laennec's cirrhosis, the pathologic changes in the liver include scarring about the portal radicles. Probably as a result of this, in more than half of the patients with this disease, clinical evidences of obstruction of the portal circulation appear. In most patients with cirrhosis there are obvious manifestations of hepatic dysfunction at the time that the signs of portal hypertension are first noted. In a smaller number of patients, the portal hypertension is first recognized at a time when other evidences of hepatic disease are either mild or absent. These patients clinically resemble those in whom portal hypertension is the result of extrahepatic obstructive lesions.

In the present study, the histories of patients with portal hypertension have been reviewed. It was possible to delineate a group of patients in whom evidence of long-standing obstruction of the portal veins was the predominant manifestation of hepatic disease. The principal symptoms suffered by these patients were repeated hematemeses and the immediate after-effects of hemorrhage. Between episodes of hematemesis, the patients were usually remarkably well. In these selected patients, the manifestations of parenchymal hepatic disease were extraordinarily mild. However, histologic examination of the liver usually showed unequivocal morphologic evidence of portal cirrhosis, indistinguishable from that seen in patients with the typical clinical course of this disorder. On the other hand, in no instance was long-standing obstruction of the portal circulation by an extrahepatic lesion followed by evidences of hepatic disease.

*These studies were conducted under contract with the Office of Naval Research, U. S. Navy.

On clinical grounds these patients with cirrhosis often could not be distinguished readily from patients with extrahepatic obstruction of the portal circulation. Nevertheless, certain features will be described which helped to differentiate between extrahepatic and intrahepatic portal obstruction.

The clinical diagnosis made in these patients with portal hypertension was often "Banti's syndrome." The patients described by Banti (1, 2) had severe anemia and splenomegaly for many years, followed successively by gastro-intestinal symptoms, jaundice, and ascites. At autopsy, cirrhosis of the liver was observed. The data to be presented demonstrate that the clinical course of the patients under consideration did not resemble that described by Banti.

DESCRIPTION OF THE CASE MATERIAL

The case histories of approximately 300 patients with manifestations of portal hypertension were reviewed. These manifestations include splenomegaly and the presence of enlarged collateral communications between the portal and systemic venous beds. All of these patients had been hospitalized at the Johns Hopkins Hospital between January 1, 1937 and April 1, 1950. Most of them had obvious evidences of hepatic disease at the time that portal hypertension was first apparent. Such patients were excluded from this study. There remained 48 cases in which there was little or no evidence of liver disease when symptoms of portal hypertension became manifest. The majority of these patients were examined by one or another of the authors. Of these 48 patients, 10 were not examined either at operation or autopsy, and were therefore eliminated from consideration. Fifteen others were subjected to laparotomy, and the liver was described as grossly normal, but no histologic examination was made. Occasionally, Laennec's cirrhosis is demonstrable histologically in sections of liver which appear normal to gross examination. For this reason these 15 cases were also excluded from this study. Of the remaining 23 patients, 15 had cirrhosis of the liver demonstrated histologically in 10, and grossly, at operation, in the other 5. In 8 of the patients with evidences of portal obstruction, the liver was normal by histologic examination. The data to be presented are based on these 23 cases.

A. Portal hypertension associated with cirrhosis

In this selected group of 23 patients with portal hypertension, there were 10 males and 5 females with hepatic cirrhosis. All the patients were native Americans except for two who were born in Italy, and one in Poland. All except one were white, although 40 per cent of the patients admitted to the Johns Hopkins Hospital are colored. Five of the males and 2 of the females gave a history of excessive alcoholic intake. In the remaining 8, alcoholism seemed improbable. Three patients were known to have had syphilis, treated in each case with arsenical compounds; two of these patients were alcoholics. All 3 had persistently positive serologic tests for syphilis. One patient had been briefly but heavily exposed to carbon tetrachloride 3 years before the appearance of the first symptom. One patient was found to have had diabetes mellitus 6 years before the first evidence of portal hypertension.

The most prominent symptom in all these 15 patients was hemorrhage from the gastro-intestinal tract. In 5 of the patients, hematemesis or melena was the first symptom. In the others, gastro-intestinal hemorrhage was preceded by months or years by other, perhaps related symptoms. In 4 patients, symptoms suggestive of an episode of hepatitis preceded gastro-intestinal bleeding by one to 27 years. In 4 other patients, episodes of nausea, vomiting, abdominal discomfort, or gaseous distention occurred one to 11 years before hemorrhage. However, these patients were in no case incapacitated by these symptoms more than transiently. One patient noticed the appearance of vascular spiders a year before his first hematemesis.

The age of the patients at the time of the first gross *gastro-intestinal hemorrhage* ranged from 23 to 58 years of age. In 12 of the 15 patients, gastro-intestinal bleeding was first evident between the ages of 23 and 48. In 12 cases, the patients had hematemeses, and in the other 3, melena during this first episode. The frequency with which hemorrhage recurred was extremely variable, the free intervals in untreated patients being as long as 6 years. Repeated hemorrhages tended to recur over a period of weeks or months, only to be followed by prolonged remissions. Gastro-intestinal hemorrhage appeared suddenly, and without any apparent inciting event, in all but one patient. In this patient,

hematemesis occurred once after an alcoholic bout, and once after an automobile accident; but this same patient had other hematemeses in the absence of any obvious inciting incident.

Other symptoms were not prominent in these patients with cirrhosis but it will be remembered that the group was selected on the basis of this fact. Eight of the patients had intermittent abdominal distress at some time during their illness when bleeding was not apparent. One patient had epistaxes just preceding her first gastro-intestinal hemorrhage, although her platelet count was normal. One year before his first hematemesis, one patient had transient ascites, thought at the time to be associated with glomerulo-nephritis.

The *spleen* was enlarged in every case. In 3 patients, the spleen was noted to be palpable from one to 11 years prior to the first gastro-intestinal hemorrhage. In 4 patients, a palpable spleen was observed immediately after the first episode of gastro-intestinal bleeding; and in 8 others, splenic enlargement was first discovered from one month to 14 years later. The spleen was usually 3 to 5 cm. below the costal margin when it was first palpated, and tended to increase in size. The weight of the spleen was determined after splenectomy or at autopsy in 8 patients. The spleens ranged in weight from 390 to 1200 grams, the average being approximately 750 grams.

The *liver* was palpable in every patient. The hepatic enlargement was not impressive when the patient was first seen, but in some cases progressive enlargement appeared to occur. The liver was examined at autopsy in 3 cases, and weighed 1700, 1800, and 2350 grams, respectively.

Clinical *jaundice* was minimal in the group under consideration. Five patients had transient icterus of mild degree on one or more occasions during their illness. In 7 patients, transient *ascites* was demonstrable. In each of these patients, the ascites followed episodes of massive gastro-intestinal hemorrhage, and lasted from a few weeks to as long as 8 months. One of these 7 patients also had transient ascites after an upper respiratory infection, and was thought at the time to have acute glomerulo-nephritis. Another patient had an episode of ascites after a laparotomy. One of the 7 patients also had transient *hydrothorax* coincident with an episode of ascites. In none of the patients was edema demonstrable.

Prominent *abdominal collateral veins* were observed in 7 of the 15 patients. Seven of the patients were noted to have hemorrhoids. However, hemorrhoids are exceedingly common in persons the same age group as these patients with cirrhosis. *Vascular spiders* were described in 8 patients. In one of these, the spiders were observed by the patient a year before his first gastro-intestinal hemorrhage. In the others, the spiders were noted either at the time of the first episode of bleeding or in the succeeding years. The presence of *palmar erythema* was recorded in 5 patients.

A transient elevation of temperature lasting several days regularly followed gastro-intestinal hemorrhage. In contrast to patients with decompensated cirrhosis, these patients did not have fever at other times. At least a quarter of patients with cirrhosis who have symptoms referable to parenchymal damage of the liver have otherwise unexplained fever (3).

The tongue of one male patient of thirty-eight had a beefy appearance transiently, about one year after his first hematemesis. Another patient, a female of thirty-nine, was noted to have papillary atrophy of the tongue. Neither of these patients gave a history of alcoholism. One patient was observed to have clubbed fingers, and another had excessive incurvature of the finger nails. One patient had bilateral inguinal herniae, and another an incisional hernia. It is noteworthy that neither of these patients had ascites.

The diagnosis of portal hypertension was substantiated by demonstration of esophageal varices by X-ray examination in 10 of 14 patients studied. Esophagoscopy revealed the presence of varices in each of 7 patients, including 2 in whom X-ray studies were negative, and one in whom x-ray examination was not performed. Esophageal varices, then, were observed to be present in 13 of the 15 patients with cirrhosis.

Blood studies demonstrated a variable degree of anemia, depending upon the blood loss in the period preceding examination. In those patients whose blood was studied after recovery from hemorrhage, a normal red blood cell count was the rule. In no case was a persistent macrocytic anemia present, although in 2 instances a transient macrocytosis was observed. The fragility of the red cells to hypotonic sodium chloride solution was normal in each of 5 patients tested. In 14 of the

patients, white blood cell counts were made at a time remote from hemorrhage. In each instance, the count was less than 5,000 cells per mm^3, and was 2,000 or less in 6 patients. In the 15th patient, the only white blood cell count was determined immediately after hematemesis and was 11,200. Immediately following hemorrhage, moderate leukocytosis was often observed. After splenectomy, the white blood cell count rose to normal levels in 7 of 8 patients studied. The differential count was not abnormal except that in 7 of the patients, mild eosinophilia, usually of 6 to 7 per cent, was present from time to time. Few studies of blood platelets were recorded. The platelets were fewer in number than 100,000 per mm^3 in 5 of 8 patients in whom counts were recorded prior to splenectomy, but in no instance was thrombocytopenia associated with purpura. In patients whose spleens had been removed, the platelet count was usually normal. The bleeding time was recorded in 10 patients with cirrhosis, and was normal in each instance. In each of 9 patients, the clotting time was normal.

Liver function was studied by a variety of tests. The serum bilirubin was measured in each patient. In 4 of these, the highest recorded value was less than 1.0 mg. per 100 ml. In the other 11 patients, the serum bilirubin was intermittently elevated. The highest concentration of bilirubin, 4.8 mg. per 100 ml., was observed in a patient who six years before had had an episode of what appeared to be homologous serum jaundice following transfusion for hematemesis. Bromsulfalein excretion was measured in 14 of the 15 patients with cirrhosis, and was impaired in every case at some time. However, there were remarkable fluctuations in the degree of bromsulfalein retention, and in 5 of the patients, normal values were observed on occasion. This fluctuation may have been due in part to variable techniques during the 13 years of this study, although in most cases the test was performed by injecting 5 mg. of bromsulfalein per kg. of body weight, and measuring the concentration in the serum 30 minutes thereafter.

The serum albumin and globulin concentrations were measured in each of the patients. The concentration of albumin was less than 4.0 gm. per 100 ml. in the weeks following gastro-intestinal bleeding in 12 of the patients, and less than 3.0 gm. per 100 ml. in three. At other times, the albumin values were 4.0 gm. or more in the patients tested. The globulin concentration was elevated above 3.0 gm. per 100 ml. at

some time in 7 of the patients, and exceeded 3.5 gm. per 100 ml. in 3 cases. Following hematemesis, the concentration of globulin tended to fall. Cephalin flocculation tests were performed in 8 patients, and were positive 3 plus or higher, in 4 cases. However, in 2 of the 4 patients with positive tests, negative tests were recorded at other times. The thymol turbidity was measured in 8 patients. In 6 patients it was elevated to 5.0 or more Maclagen units and in 3 cases it exceeded 10.0 units. The results of this test, too, showed considerable variation from time to time and in every patient in whom repeated determinations were made, both normal and abnormal values were obtained.

The alkaline phosphatase activity in serum was determined in 10 of the 15 patients. In 6 of these patients, the activity was in excess of 5.0 Bodansky units. The highest value recorded, 14.9 Bodansky units, was in a patient who had consistently elevated phosphatase activity. Two patients who had elevated alkaline phosphatase values had normal enzymic activity at other times.

The prothrombin time was measured in 12 of the patients with cirrhosis. It was prolonged beyond the range of normal in 7 cases. In one of these patients, the prothrombin time gradually returned to normal over a period of 3 years. The non-protein nitrogen was normal in every case, except that moderate elevations occurred in the period immediately following hemorrhage.

Seven of the 15 patients with cirrhosis are known to be dead. Two of these patients died within 24 hours after splenectomy. In one of these patients, a porto-caval anastomosis was also performed. Three patients died of the results of hematemesis from esophageal varices and 2 of hepatic insufficiency. Of the 7 fatal cases, 4 deaths occurred within 2 years after the first gastro-intestinal hemorrhage, and the others, 6, 12, and 16 years thereafter. It is impressive that 6 of the 15 patients were alive 6 years after the first recognized gastro-intestinal hemorrhage, and 3 survived 12 or more years (Fig. 1). The prognosis of these patients is in striking contrast to that of unselected patients with cirrhosis who have gastro-intestinal bleeding. In one series of such patients, 70 per cent died within one year after the initial hematemesis (3).

Liver tissue was available for study in 10 cases. In 7 instances, biopsy specimens alone were examined, in 2, autopsies were performed,

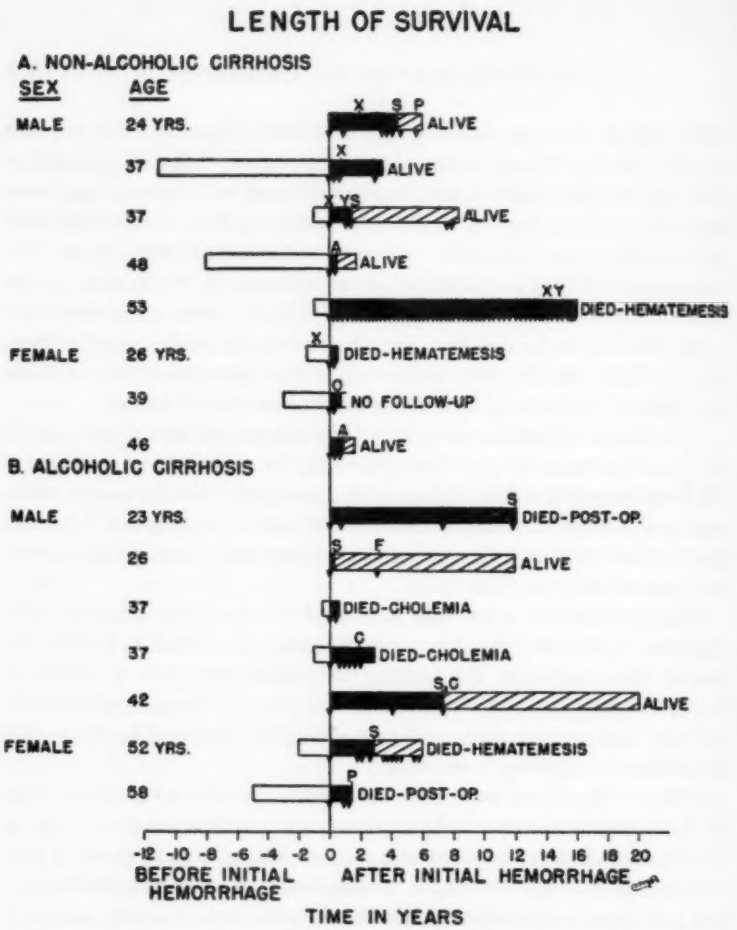


FIG. 1. The length of survival of 15 patients with cirrhosis of the liver. These patients were selected because they had manifestations of portal hypertension with little or no evidence of hepatic dysfunction. In Fig. 1 and 2, the age of the patient at the time of the first episode of gastro-intestinal hemorrhage is recorded.

The following key is used in Fig. 1 and 2: *Horizontal bars:* Clear area—Period of symptoms preceding first recognized gastro-intestinal hemorrhage. Solid area—Period after first episode of bleeding, but before splenectomy. Hatched area—Period after splenectomy. Saw-toothed border—Periods during which gastro-intestinal hemorrhage occurred.

The *letters above the bars* represent the following operative procedures: A. Spleno-renal anastomosis. B. Ligation of vessels of upper two-thirds of stomach and diaphragmatic portion of esophagus. C. Coagulation and ligation of gastric veins and omentopexy. E. Division of esophagus and its re-anastamosis to stomach. F. Fulgeration of varices. G. Total gastrectomy. L. Ligation of esophageal varices. O. Omentopexy. P. Porto-caval anastomosis. R. Removal of gangrenous bowel. S. Splenectomy. V. Injection of esophageal varices. X. Exploratory laparotomy.

and in one, both biopsy and autopsy materials were available. The specimens for biopsy were all obtained at laparotomy. In 9 cases, definite portal cirrhosis was present. In the tenth case, only a small subcapsular specimen of tissue was available for examination. In this specimen, fine scars were seen radiating from the capsule and dividing the parenchyma into nodules. However, a small part of the tissue present appeared normal. It is well known that a biopsy specimen obtained from the region of the capsule may show subcapsular scars indistinguishable from cirrhosis. For this reason, the unequivocal diagnosis of portal cirrhosis did not seem justified in this case.

The degree of cirrhosis varied in the specimens studied. In 2 there were marked scarring and evidence of active nodular regeneration of hepatic cells which varied considerably in size and staining and sometimes contained large and bizarre nuclei. In other instances, changes of a similar nature were present to a lesser degree; in these cases, the cirrhosis appeared mild, and parenchymal cells which appeared normal were present in great number. In 7 of the patients, no evidences of fatty infiltration of the liver were present, and in the remaining 3, the fatty infiltration was very slight.

In one case, examined at autopsy, acute atrophy of the parenchymal cells was noted in the central areas of the hepatic lobules. This was associated with dilatation and congestion of the central sinusoids. These changes were typical of the so-called Zahn "infarct" (4), and in this case, fresh thrombi were found in the hepatic artery and in the branches of the portal vein.

In general, the scars in the specimens examined were thin. However, they disrupted the normal architecture of the liver except in the equivocal case described. Bile duct proliferation was minimal or absent. The preservation of large areas of intact hepatic cells was striking, but this was not surprising in view of the manner in which these cases were studied.

Specimens of the spleen were available for study in 7 cases. The spleens appeared to be more firm than normal. The capsules were thickened and the blood vessels were prominent. The malpighian corpuscles were usually indistinct. Histologically, the spleens of all these cases were similar and displayed the changes usually observed in cases of cirrhosis. The sinusoids were dilated and the lining cells

were prominent. Occasionally, large mononuclear cells lay free in the lumen. The sinusoidal walls appeared to be greatly thickened and fibrosed. However, appropriate stains for connective tissue demonstrated that most of these changes were the result of condensation of thin fibers of connective tissue. Proliferation of connective tissue was frequently very prominent in the trabeculae about blood vessels and in the capsule, and fibrous tissue extended from these regions into the surrounding pulp. The pulp was often quite cellular, containing a variety of leukocytes, and many large mononuclear cells, presumably reticulum cells. These mononuclear cells were often elongated, and were similar in appearance to fibroblasts. In none of the cases was extramedullary blood formation observed. In one specimen, hemorrhages were present in the trabeculae and beneath the capsule, but in no instance was a typical siderotic nodule seen. Prominent malpighian corpuscles with germinal centers were present in 3 cases.

All of the spleens studied, then, showed alterations compatible with hypertension of the splenic vein. These changes were typical of those seen in portal cirrhosis. It is of interest, however, that the changes in these 7 cases were more prominent and more uniform than those present in sections of the splenic tissue of 20 *unselected* cases of cirrhosis of the liver examined at autopsy.

B. Portal hypertension resulting from extrahepatic obstruction

In 8 patients, there were manifestations of portal hypertension in the absence of histologic evidence of liver disease. In 2 of these patients, the cause of the obstruction was demonstrated at autopsy. One patient had extensive scarring of the hilum of the liver, associated with thrombosis and recanalization of the portal vein. Another had severe stenosis of the portal vein. In the other 6 patients, the nature of the obstruction is unknown, since the patients are still alive.

Five of the 8 patients with extrahepatic disease were male and 3 female. All were white, and all were American born, although one was of Italian stock. None of these patients was an alcoholic or known to have syphilis. One patient was said to have been kicked in the abdomen 8 days prior to his first hematemesis. Another patient had severe colitis at the age of 2 or 3 months, about 9 years before her first gastrointestinal hemorrhage, and one patient had had a thyroidectomy for hyperthyroidism 2 years before her first hematemesis.

As in the patients with cirrhosis, gastro-intestinal hemorrhage was the major symptom in this group. In 5, a hematemesis was the patient's first symptom. One patient had symptoms of anemia and was found to have melena. Another was discovered to have a palpable spleen at the age of 5, when she was examined because of a brief episode of abdominal pain, but had no further symptoms until a hematemesis occurred 12 years later. The eighth patient never regained his strength after an episode of pneumonia, 4 months before his first hematemesis at 7 and a half years of age.

The first *gastro-intestinal hemorrhage* occurred in 7 of the 8 patients before the age of 18, and in one patient, at 37. Five of these patients were operated upon within a few months of the first bleeding episode, so that it is not possible to evaluate the frequency with which hemorrhage would have recurred during the natural history of their disease. However, in 2 of 3 patients who were not subjected to immediate surgery there were free intervals as long as 14 months in one patient and 3 years in the other. These same patients, however, had frequently repeated bleeding episodes before and after these prolonged free intervals. Hematemesis almost always occurred without relation to any evident exciting cause. However, in one patient hematemesis appeared during the first stage of labor, in another, following a bout of uncontrollable laughter, and in a third, the day after the extraction of a tooth. In each of these patients, hematemesis occurred on other occasions without obvious immediate cause.

Symptoms other than those associated with gastro-intestinal hemorrhage were strikingly absent in these patients. Gastro-intestinal symptoms were present only in relation to the bleeding episodes. One patient had occasional epistaxes during the 6 months before her first hematemesis. This was associated with thrombocytopenia.

The *spleen* was palpable in every patient. In one patient, splenomegaly was discovered 12 years before the first bleeding episode. In 4 patients, the spleen was palpated at the time of the first gastro-intestinal hemorrhage. In the remaining 3 patients, splenomegaly was first observed 1 to 8 years after the first hematemesis. In 2 of the patients, the spleen decreased in size after a bout of hematemesis. As in the patients with cirrhosis, the spleen tended to increase in size with time, so that in one patient it was felt at the level of the iliac crest, and was 5 to 12 cm. below the costal margin in 3 others. The

weight of the spleen was available in 5 cases. It was 478 gm. in a boy of 7 and a half, 335 gm. in an 8 year old boy, 385 gm. in a patient of 14, and 750 and 851 gm. in 2 patients of 17. In the other 3 cases the spleen was described as enlarged when it was removed at operation, but the weight was not recorded.

In contrast to the patients with cirrhosis, none of the patients in this group had enlargement of the *liver* on physical examination. In the 2 patients examined *post mortem*, at 19 and 20 years of age, the liver weighed 1150 and 1310 gm., respectively.

Clinical *jaundice* was not observed in these patients. Transient *ascites* occurred in 4 patients, in each instance after massive gastro-intestinal hemorrhage. In one of these patients, ascites recurred on 4 occasions, and in another, twice. Two of the episodes followed an abdominal operation, but in both cases the patient had had a severe hematemesis just prior to operation. The episodes of ascites lasted only a few weeks each time. In one boy of 7, the ascites was accompanied by transient peripheral edema. A female patient, following hematemesis at the age of 40, had transient *edema* of the ankles and face, although these symptoms were not present with numerous other bouts of severe bleeding before and after this episode. None of the patients had prominent *abdominal veins* or hemorrhoids, although collateral veins on the abdominal wall have been observed in patients with extrahepatic portal obstruction other than those reported here. In 2 patients, *vascular spiders*, not distinguishable from those commonly associated with hepatic disease, were noted. One patient developed many such lesions at the age of 23, 13 years after his first episode of gastro-intestinal bleeding. The other was observed to have vascular spiders at the age of 41, 4 years after her first bleeding episode. None of the patients had *palmar erythema*. In 7 of the patients, fever did not occur except in the period immediately following gastro-intestinal hemorrhage. One child had intermittent low grade fever from the time he was one and a half years of age until he was about 7. No other significant physical findings were noted.

Esophageal varices were demonstrated in all of the 8 patients by X-ray examination, and in each of 3 patients subjected to esophagoscopy.

In the period following hemorrhage, each of the patients had severe

anemia. However, in 6 patients studied at a time removed from a severe hemorrhagic episode, the hematocrit, red blood cell count and hemoglobin were normal. Seven of the 8 patients were known to have leukopenia prior to splenectomy, and white blood cell counts of 3000 per mm^3 or less were obtained on occasion in 5 of these 7. None the less, following hemorrhage, a moderate leukocytosis was regularly noted.

As in some of the patients with cirrhosis, transient eosinophilia of 6 to 13 per cent was present in 5 of the 8 patients. The blood platelets were reduced in number before splenectomy in 3 of the 5 patients in whom counts were recorded. In these 3 patients, the counts ranged from 40,000 to 100,000 per mm^3; after splenectomy, the number of platelets rose. However, in one of the patients with thrombocytopenia, the platelet count was only 84,000 per mm^3, 15 months after splenectomy. The bleeding time, determined in 4 cases, and the clotting time measured in 5 cases, were normal.

Tests of liver function were performed in every patient. The serum bilirubin was determined on one or more occasions in each of the 8 patients. In 4, the serum bilirubin was never observed to exceed 0.8 mg. per 100 ml. In two others, values as high as 1.1 mg. per 100 ml. were recorded, a concentration at the upper limit of normal in the hospital's laboratory. In the remaining 2 patients, the serum bilirubin rose transiently to 1.5 to 3.5 mg. per 100 ml. respectively, the latter value being observed after hematemesis.

Bromsulfalein excretion tests were performed in all of the patients. As in the group of patients with cirrhosis, remarkable fluctuations were observed in the degree of retention of bromsulfalein when the test was performed repeatedly in the same patient. In 4 of the patients, definitely impaired bromsulfalein excretion was observed on one or more occasions, although in 3 of these patients normal values were also obtained at other times. The degree of retention of the dye appeared to be greater at a time when anemia was present. As in the patients with cirrhosis, low albumin values were frequently recorded during the period after gastro-intestinal bleeding, and values less than 4.0 gm. per 100 ml. were observed in 7 of the 8 patients at these times. Normal values were obtained in the 5 patients whose blood was studied at times remote from hemorrhage. Abnormally high globulin

values were not observed in any patient. The cephalin flocculation test was performed in 6 cases. It was transiently positive, 2+ to 3+, in 3 patients, but was normal in the same patients on other occasions. Thymol turbidity was elevated to 5.0 or more Maclagen units in 2 of the 6 patients in whom this test was performed, but never exceeded 9 units. Normal values for the thymol turbidity test were obtained at other times in the two patients whose tests were positive.

The alkaline phosphatase activity was measured in 6 of the 8 patients. In 2 patients, the value exceeded 4.7 Bodansky units. In one of these patients, in a single determination an activity of 5.4 Bodansky units was followed on a subsequent occasion by an activity of 3.0. In the other patient, a child of 7 and a half years, the alkaline phosphatase activity was 6.2 and 9.0 units on 2 occasions, normal values in children (5).

The prothrombin time was determined in 5 patients. In 3 patients, normal values were obtained. In the other 2 patients, transient slight prolongation of the prothrombin time was observed on occasion, but normal values were recorded at other times. As in the patients with cirrhosis, the non-protein nitrogen was normal in every case except during the period after gastro-intestinal hemorrhage.

Two of the patients with extrahepatic portal obstruction have died. One died following a bout of severe gastro-intestinal bleeding, 11 years after her first hematemesis. The other died 6 years after his first episode of bleeding. Six weeks before his death, the patient was operated upon for resection of gangrenous bowel, associated with mesenteric venous thrombosis.

The remaining 6 patients are known to be alive 1 month, 2, 7, 10, 18, and 22 years after their first gastro-intestinal hemorrhage (Fig. 2).

Specimens of liver were examined histologically in every case. The tissues were obtained at autopsy in 2 instances including one in which a biopsy specimen was also available. In the other 6 cases, biopsy specimens of the liver were examined. The biopsies were all obtained at laparotomy.

In the sections available, the hepatic tissue either appeared normal or showed such trivial changes as slight fatty infiltration or a slight increase in the number of periportal lymphocytes. In one case, a

significant increase in hyaline periportal fibrous tissue was observed, associated in some areas with accumulation of lymphocytes and possibly with proliferation of bile ducts. However, the connective tissue in this specimen did not extend from the portal areas into the liver lobule, and the architectural pattern of the liver was normal. These changes suggested the possibility that at one time this liver may

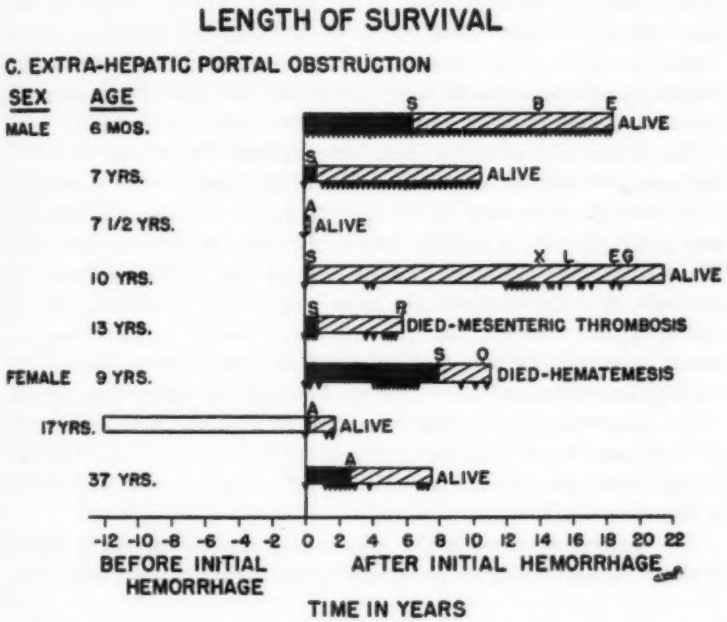


FIG. 2. The length of survival of 8 patients with portal hypertension unassociated with hepatic disease. The symbols used are described in the legend for Fig. 1.

have been damaged. However, it was the opinion of the pathologists who examined this tissue that the changes were not those of cirrhosis. It is of interest that this specimen was obtained from a 14 year old boy who had had recurrent hematemeses since the age of 6 months. This patient, who is now 19 years old, has never displayed clinical or laboratory evidence of hepatic dysfunction.

Two of the patients were examined at autopsy. In one of these, an old re-canalized thrombus of the splenic vein had been found at the time splenectomy was performed. Five and a half years later, when the patient died, he was observed to have extensive scarring of the hilum of the liver, associated with thrombosis of the portal and mesenteric veins, and recanalization of the portal vein. A recent infarct of the intestine was described. In the second patient, the portal vein was severely stenosed close to its entrance to the liver. On microscopic examination of the tissue in this region, many thin-walled dilated vessels, and several large thrombosed and partially recanalized veins were seen. In both patients, the liver appeared normal.

The spleens of 6 of the patients were studied. The organs were firm, the capsules were usually thickened, and the vessels were prominent. The histologic appearance of the spleens was remarkably uniform, and was strikingly similar to that seen in the cases of cirrhosis described. The splenic pulp was possibly more cellular than in the patients with cirrhosis, and the hemorrhagic areas were more prominent. In one case a typical siderotic nodule was present, and in 2, there was evidence of extramedullary blood formation. The fibrosis around the malpighian corpuscles, described by Banti in his cases, was not observed. However, in 4 of the 6 spleens studied, the malpighian corpuscles were large, and the germinal centers prominent. This appearance may have been a reflection of the young age of these patients at the time of splenectomy.

The changes observed in the spleens of these patients were typical of those encountered after prolonged hypertension of the splenic vein.

DISCUSSION

Obstruction of the portal circulation may be due either to hepatic or extrahepatic lesions. In those patients who have hepatic disease, the clinical manifestations of parenchymal liver damage are usually evident. There are, however, patients with cirrhosis of the liver in whom evidences of parenchymal hepatic disease are slight, although portal hypertension is present. The current study indicates that the clinical differentiation of such patients from those with extrahepatic portal obstruction is difficult. Certain criteria, however, are helpful in making this differentiation.

The symptoms of patients with portal hypertension were similar, regardless of the etiology. All of the patients under consideration bled from the gastro-intestinal tract. Episodes of gastro-intestinal bleeding usually occurred without any apparent inciting event, although premonitory symptoms of abdominal distress were frequently present for several hours or a day. Ordinarily, the gastro-intestinal bleeding recurred in bouts lasting several weeks or months, followed by free periods of months or even years. In the period immediately following severe gastro-intestinal bleeding, transient ascites was common. Ascites at this time was observed with equal frequency in patients with extrahepatic and intrahepatic portal obstruction. This is contrary to the experience of Smith and Farber (6), who reported that ascites was not detected in any of 15 patients with extrahepatic portal obstruction. The ascites was usually not sufficiently incapacitating to require paracentesis, and ordinarily receded after several weeks. The ascites which occurred immediately following hemorrhage was thus of a more benign nature than that occurring in the usual patient with cirrhosis.

The spleen was palpable in all of the patients with portal hypertension, and tended to increase in size with time. In the period immediately following severe gastro-intestinal hemorrhage, the spleen was observed to decrease in size in a few cases. This may indeed have occurred more frequently than was noted, for there are many reports in the literature of a transient decrease in the size of the spleen after hematemesis (6, 7, 8, 9).

Esophageal varices were demonstrated in 21 of the 23 patients examined, either by X-ray or esophagoscopy. However, superficial collateral veins on the abdominal wall were seen in only about half the cases, and none of the patients had a caput medusa. Two patients had epistaxes. One of these had thrombocytopenia, but in the other, the platelet count was normal. In similar cases epistaxis in the absence of thrombocytopenia has also been described by Rousselot (9). Vascular spiders, often seen in patients with hepatic disease, were also present in 2 patients with extrahepatic portal obstruction.

Immediately following gastro-intestinal hemorrhage, anemia was the rule. However, in the period between hemorrhages, the red blood cell count, hemoglobin and hematocrit were normal. This is in con-

trast to the chronic anemia observed by Banti (1, 2) in his patients. Leukopenia was regularly observed before splenectomy, but the patients responded to such stimuli as hemorrhage or infection with leukocytosis. After splenectomy, the white blood cell count usually returned to normal. Transient, mild eosinophilia was frequently present, both before and after splenectomy, and in patients with or without hepatic disease. Thrombocytopenia was frequent in patients with portal hypertension, but was rarely of sufficient degree to cause hemorrhagic manifestations. The platelets usually rose to normal after splenectomy.

Certain tests of liver function were not helpful in distinguishing between intra- and extrahepatic portal obstruction. The results of the bromsulfalein excretion test varied from time to time, but excretion was impaired in patients with or without hepatic disease. Bradley (10) and others have demonstrated that the excretion of bromsulfalein is a function of the blood flow through the liver. Possibly the impairment of bromsulfalein excretion in patients with extrahepatic portal obstruction is related to the diminished blood flow through the liver. Similarly, the cephalin cholesterol flocculation test and thymol turbidity test were frequently positive and the prothrombin time was occasionally prolonged in both groups of patients.

Several features were observed which were useful in differentiating between intra- and extrahepatic portal obstruction (Table I). The age of the patient at the time that gastro-intestinal bleeding was first recognized was of some aid in diagnosis. All the patients with cirrhosis of the liver were 23 years or older at the time of appearance of their first symptom. On the other hand, 7 of the 8 patients with extrahepatic obstruction were 17 or younger at the time of the first episode of gastro-intestinal bleeding, and 13 or less at the time that the earliest evidence of portal obstruction was recognized. The patients' symptoms were of little help in differentiating intra- and extrahepatic disease. None the less, it was significant that aside from the effects of repeated gastro-intestinal hemorrhages, the patients with extrahepatic portal obstruction were singularly free of symptoms. In contrast, several patients with hepatic disease had histories suggestive of an episode of hepatitis some time before the first gastro-intestinal hemorrhage, and vague gastro-intestinal symptoms were present between the episodes of bleeding in many of the patients with cirrhosis.

TABLE I

The Differentiation Between Extrahepatic and Intrahepatic Portal Obstruction

	PORTAL CIRRHOSIS	EXTRAHEPATIC PORTAL OBSTRUCTION
Number of cases	15	8
Sex incidence	10♂, 5♀	5♂, 3♀
Age at initial gastro-intestinal hemorrhage	23 years or older	7 of 8 patients 18 years or younger
Past History:		
Alcoholism	7 of 15 cases	0 of 8 cases
Syphilis	3 of 15 cases	0 of 8 cases
Arsenical therapy	3 of 15 cases	0 of 8 cases
Exposure to CCl_4	1 of 15 cases	0 of 8 cases
Possible hepatitis	4 of 15 cases	0 of 8 cases
Abdominal trauma	0 of 15 cases	1 of 8 cases
Symptoms:		
Hemorrhage from gastro-intestinal tract	15 of 15 cases	8 of 8 cases
Gastro-intestinal distress at times remote from hemorrhage	8 of 15 cases	0 of 8 cases
Signs:		
Palpable liver	15 of 15 cases	0 of 8 cases
Palpable spleen	15 of 15 cases	8 of 8 cases
Ascites after gastro-intestinal hemorrhage	7 of 15 cases	4 of 8 cases
Ascites at times remote from hemorrhage	2 of 15 cases	0 of 8 cases
Jaundice	5 of 15 cases	0 of 8 cases
Vascular spiders	8 of 15 cases	2 of 8 cases
Palmar erythema	5 of 15 cases	0 of 8 cases
Laboratory Data:		
Anemia at times remote from hemorrhage	0 of 15 cases	0 of 8 cases
Leukopenia before splenectomy	14 of 15 cases	8 of 8 cases
Elevated serum bilirubin	11 of 15 cases*	2 of 8 cases*
Hypoalbuminemia at times remote from hemorrhage	0 of 15 cases	0 of 8 cases
Hyperglobulinemia	7 of 15 cases*	0 of 8 cases
Positive cephalin flocculation test	4 of 8 cases*	3 of 6 cases*
Positive thymol turbidity test	6 of 8 cases*	2 of 6 cases*
Increased alkaline phosphatase activity	6 of 10 cases*	0 of 6 cases
Prolonged prothrombin time	7 of 12 cases*	2 of 5 cases*
Abnormal bromsulfalein retention	14 of 14 cases*	4 of 8 cases*

* In many of the patients in whom these tests were positive, normal values were obtained on other occasions.

A major feature differentiating the 2 groups of patients was the size of the liver on physical examination. It is noteworthy that the liver was palpable in all of the patients with cirrhosis, while the liver was not enlarged in any of the patients with extrahepatic obstruction. Other features of the physical examination were not helpful except that palmar erythema was observed in some of the patients with cirrhosis and in none of those without liver disease. However, palmar erythema is occasionally seen in normal individuals as well as in patients with a variety of diseases, so that its presence need not indicate the existence of hepatic damage.

As has been noted, ascites lasting for a few weeks was present in both groups of patients following gastro-intestinal hemorrhage. However, ascites unrelated to bleeding did not occur in patients with extrahepatic portal obstruction. Therefore, the occurrence of ascites at a time remote from hemorrhage provides strong evidence for the presence of hepatic disease.

Laboratory studies were of some help in distinguishing between intra- and extrahepatic disease. Transient elevation of the concentration of bilirubin in serum was seen in both groups of cases. However, the elevation of bilirubin was more frequent and of greater magnitude in the patients with cirrhosis. The concentration of albumin in the serum was decreased in both groups of patients in the weeks following severe gastro-intestinal hemorrhage, and returned to normal when the patients had recovered from the effects of bleeding. However, the serum globulin concentration was elevated in 7 of the 15 patients with cirrhosis, and in none of the 8 patients with extrahepatic obstruction, a difference that is statistically significant. Finally, the alkaline phosphatase activity was increased above normal in 6 of the patients with cirrhosis, but in none of the patients with extrahepatic portal obstruction.

In only 2 of the 8 patients with extrahepatic portal obstruction was it possible to determine the nature of the lesion causing obstruction, and in these cases only at autopsy. It is seldom possible for the surgeon to examine the portal and splenic vein adequately during laparotomy. Indeed, a careful search is often necessary at autopsy to demonstrate the site of the obstruction (11, 12). The causes of obstruction of the portal and splenic vein have been reviewed by Moschcowitz

(13). Among these conditions are congenital stenosis of the portal or splenic vein, or cavernomatous transformation of these vessels. Or there may be thrombosis of the portal or splenic vein, or impingement on these vessels by inflammatory adhesions, neoplasms, or other changes in adjacent structures.

In no instance has a patient with extrahepatic portal obstruction been observed to develop histologic evidence of cirrhosis of the liver. In the present series, several of the patients were known to have had signs of portal obstruction for many years prior to microscopic examination of the liver. Indeed, no evidence of cirrhosis was observed in a patient who had had portal obstruction for 33 years (14). The absence of hepatic disease after long-standing extrahepatic portal obstruction was emphasized by Thompson (15).

In 1894, Banti (1) described a group of patients with an unusual train of symptoms. These patients were said to have enlargement of the spleen and severe anemia (1, 2). After an interval of as long as 10 or 11 years, the patients began to complain of gastro-intestinal symptoms. Sometimes the patients were icteric. The urine became scanty and contained bile and urobilin in abnormal amounts. Finally, after these vague symptoms had been present for several months, ascites appeared, the liver was said to shrink, and the patients died. At autopsy, cirrhosis of the liver and an enlarged spleen were found. Microscopically, the appearance of the spleen was similar to that seen in the cases which we have described. It seems probable that these patients had Laennec's cirrhosis with congestive splenomegaly. However, it is clear from this summary that Banti's patients did not resemble those described in the present report. For this reason the term *Banti's syndrome* appears to be inadequate to designate the symptoms and signs of these patients with portal obstruction.

During the years encompassed by the current study, 25 additional patients were admitted to the hospital with symptoms and signs indicative of portal hypertension, but without obvious parenchymal hepatic disease. Fifteen of these patients were subjected to laparotomy, at which time the liver appeared normal, but histologic examination was not made. It is known that cirrhosis may be present in a liver which appears grossly normal. Therefore, we are unable to determine whether cirrhosis was present in these patients. It is clear that on

clinical grounds one cannot always determine whether the lesion obstructing the portal circulation is intra- or extrahepatic. The data presented emphasize that a biopsy of the liver is necessary to differentiate cirrhosis from other causes of portal obstruction.

SUMMARY

In a small proportion of patients with Laennec's cirrhosis, clinical evidences of portal hypertension are first recognized at a time when other manifestations of hepatic disease are mild or absent. The case histories of 15 such patients were compared with those of 8 patients with portal obstruction in whom the liver was histologically normal.

The symptoms of these 23 patients with portal hypertension were similar regardless of the etiology. All had splenomegaly, esophageal varices were demonstrated in 21 of the 23, and all had gastro-intestinal hemorrhages. In the period immediately following severe bleeding, transient ascites was common. Anemia was observed only after hemorrhage, but leukopenia was regularly present before splenectomy, and moderate thrombocytopenia was common. The bromsulfalein excretion, cephalin flocculation, and thymol turbidity tests, and the determination of the prothrombin time often gave abnormal results both in patients with intra- and extrahepatic disease.

Certain criteria were helpful in differentiating between intra- and extrahepatic portal obstruction. All of the patients with cirrhosis were 23 years or older at the time of their first symptom, while 7 of the 8 patients with extrahepatic obstruction were 17 or younger when the first gastro-intestinal hemorrhage occurred. The patients with cirrhosis commonly had gastro-intestinal symptoms at times remote from bleeding, the liver was invariably palpable and the concentration of serum globulin and alkaline phosphatase activity were often increased above normal. In contrast, none of these abnormalities was present in patients with extrahepatic portal obstruction. It is noteworthy that in no instance was long-standing obstruction of the portal circulation by an extrahepatic lesion followed by cirrhosis of the liver.

The 23 patients described were selected from among approximately 300 patients with portal hypertension hospitalized during a 13 year period. Most of these 300 patients had obvious evidences of hepatic disease. There remained 25 patients without clinical manifestations of hepatic disease who were not included in this study. Although 15

of these patients were subjected to laparotomy, histologic examination of the liver was not made. Clinically, it is not always possible to distinguish between intra- and extrahepatic portal obstruction. The data presented emphasize that a biopsy of the liver is needed to differentiate cirrhosis of the liver from other causes of portal obstruction.

BIBLIOGRAPHY

1. Banti, G.: La Splenomegalia con Cirrosi del Fegato. Sperimentale (Comun. e Riv.), **48:** 447, (1894)—reprinted in an English translation in Med. Classics, **1:** 907, (1937).
2. Banti, G.: Splenomegalie mit Lebercirrhose. Beitr. z. path. anat. u.z. Allg. Path., **24:** 21, (1898)—reprinted in English translation in Med. Classics, **1:** 913, (1937).
3. Ratnoff, O. D., and Patek, A. J., Jr.: The Natural History of Laennec's Cirrhosis. Medicine, **21:** 207, (1942).
4. Gerlach, W.: Die Kreislaufstörungen der Leber, in Handbuch der Speziellen Pathologischen Anatomie und Histologie, Henke, F., and Lubarsch, O., editors, **5-1:** 110, Berlin, Julius Springer, (1924).
5. Bodansky, A.: Phosphatase Studies. II. Determination of Serum Phosphatase. Factors influencing the accuracy of the determinations. J. Biol. Chem., **101:** 93, (1933).
6. Smith, R. M., and Farber, S.: Splenomegaly in Children with Early Hematemesis. J. Pediatrics, **7:** 585, (1935).
7. Gilbert, A., and Lereboullet, P.: La Rate Hépatique. Compt. rend. soc. biol. Paris, **56:** 370, (1904).
8. Rolleston, H. D.: Diseases of the Liver, Gall-bladder and Bile-Ducts. Second edition, London, Macmillan and Co., Limited, (1912).
9. Rousselot, L. M.: The Rôle of Congestion (Portal Hypertension) in So-called Banti's Syndrome, J. A. M. A., **107:** 1788, (1936).
10. Bradley, S. E., Ingelfinger, F. J., Bradley, G. P., and Curry, J. J.: The Estimation of Hepatic Blood Flow in Man. J. Clin. Invest., **24:** 890, (1945).
11. Warthin, A. S.: The Relation of Thrombophlebitis of the Portal and Splenic Veins to Splenic Anaemia and Banti's Disease. Inter. Clinic, 20th Series, **4:** 189, (1910).
12. McNee, J. W.: The Spleen, Its Structure, Function, and Diseases, Lecture III. Lancet, **1:** 1063, (1931).
13. Moschcowitz, E.: The Pathogenesis of Splenomegaly in Hypertension of the Portal Circulation; "Congestive Splenomegaly." Medicine, **27:** 187, (1948).
14. Conley, C. L., and Larcom, R. C., Jr.: The Etiology of Banti's Syndrome; Further Support of the "Congestive Splenomegaly" Hypothesis. Annals Int. Med., **27:** 289, (1947).
15. Thompson, W. P.: The Pathogenesis of Banti's Disease. Annals of Int. Med., **14:** 255, (1940).

THE EFFECT OF CERTAIN CINCHONINIC ACID DERIVATIVES ON THE RENAL TUBULAR SECRETION OF PHENOL RED*

EARL H. DEARBORN

Department of Pharmacology and Experimental Therapeutics, The Johns Hopkins University School of Medicine

Received for publication July 6, 1950

A preliminary report of the inhibitory action of a small number of cinchoninic acid derivatives on the secretion of phenol red by frog kidney slices *in vitro* has been published (1). Other cinchoninic acid derivatives have now been synthesized and their ability to inhibit a water diuresis in the dog (2, 3) and to lower adrenal ascorbic acid in the rat (4) has been investigated. The 3-hydroxy-2-phenylcinchoninic acid increases the plasma concentrations found after intravenous administration of benzyl penicillin to dogs (5). It is the purpose of the present communication to report studies of the inhibition of the secretion of phenol red in dogs and an extension of the *in vitro* studies on frog kidney slices.

METHODS

The compounds used in these studies were synthesized in this laboratory by Dr. K. C. Blanchard with the exception of cinchoninic acid and 2-phenylcinchoninic acid which were kindly supplied by the the American Cyanamid Company.

The technique used for the frog kidney slices has been described (1). For the *in vivo* studies, trained female dogs were used and the urine was obtained by catheter. Phenol red was given intravenously in a dose of 6 mgm. contained in a volume of 5 ml. Urine was collected 30, 60 and 120 minutes after administration of the phenol red. To insure completeness of the urine collections the bladder was washed. The variation of control determinations of phenol red excretion in one dog is illustrated in figure 1. The drugs were usually administered intravenously as the sodium salts in bicarbonate buffered solution two to three minutes prior to the injection of the phenol red. In a few instances drugs were given orally in gelatin capsules in which case the phenol red was given one hour after administration of the drug. The effectiveness of a drug was evaluated by comparing the quantity of phenol red in the thirty and sixty minute urine specimens with similar specimens

* This investigation has been aided by grants from the U. S. Public Health Service and the Life Insurance Medical Research Fund.

taken without drug. The 120 minute excretion was of value as a measure of the persistence of the effect.

Carinamide was used as a reference standard to facilitate comparison of these data with the results of the frog experiments. The amount used as the standard of comparison was a single intravenous injection of 20 mgm. of carinamide per kgm. as the sodium salt. This dose produced an unequivocal decrease in phenol

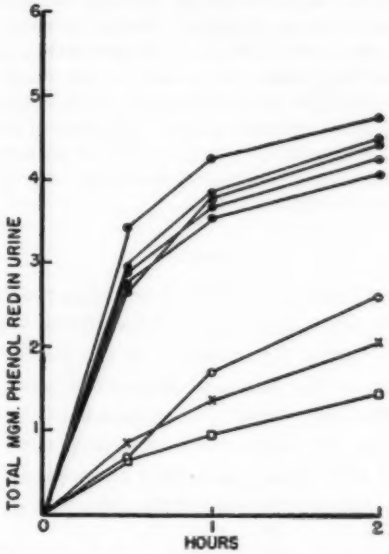


FIG. 1. THE EFFECT OF DRUGS ON THE EXCRETION OF PHENOL RED IN DOG NO. 13

●——● control; ○——○ 20 mgm. 3-hydroxy-2-phenylcinchoninic acid per kgm. intravenously; ×——× 20 mgm. carinamide per kgm. intravenously; □——□ 200 mgm. carinamide per kgm. by stomach tube followed in 45 minutes by 100 mgm. carinamide per kgm. intravenously. Phenol red was given intravenously two to five minutes after drug administration.

red excretion in every dog. Administration of large quantities of carinamide (100 to 200 mgm. per kgm. by stomach tube followed in one hour by 100 mgm. per kgm. intravenously, both in solution as the sodium salt) which gave a maximal depression of phenol red secretion was carried out in each animal. This degree of effect was assumed to approximate total inhibition of secretion. In figure 1, typical phenol red excretion curves obtained after administration of drugs are illustrated.

To establish that the effects of these drugs on the phenol red excretion were

due to a decrease in tubular secretion rather than to a decrease in glomerular filtration, the clearances of thiosulfate and phenol red were determined simultaneously. Thiosulfate was used as an indication of glomerular filtration instead of the more satisfactory creatinine because of the difficulty of simultaneous determination of creatinine and phenol red. Thiosulfate was given intravenously in doses of approximately 400 mgm. per kgm. and clearances were determined at plasma concentrations of 75 to 5 mgm. per 100 ml. Although the determination of clearances during a falling plasma concentration is less accurate than with a maintained concentration, the errors involved are not significant for the purposes of this study. Phenol red was given subcutaneously in doses of 6 to 8 mgm. per kgm. which gave reasonably constant plasma concentrations of 0.5 to 1.4 mgm. per 100 ml. Blood samples were drawn midway between collections of urine. Phenol red in plasma was determined by diluting it tenfold with 0.5 per cent sodium carbonate and reading. Thiosulfate was determined in plasma and urine by the iodate method of Gilman, Philips and Koelle (6).

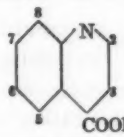
RESULTS

In table 1 are tabulated, in order of activity, the effects of the cinchoninic acid derivatives and in table 2 the effects of related quinoline derivatives in inhibiting the secretion of phenol red in frog kidney slices. Ten of the cinchoninic acid derivatives which have been reported in the preliminary paper (1) are included. The inhibitory effect of at least eight of the cinchoninic acid derivatives, when used in concentrations no more than four times the minimal inhibitory concentration, can be reversed by placing the kidney slices in fresh medium containing no drug

In table 3, estimates of the effects of the cinchoninic acid derivatives in decreasing the secretion of phenol red in the dog are given. The effect of carinamide in 20 mgm. per kgm. dosage was assigned a value of two plus; compounds definitely more active were called three plus, those definitely less active one plus and those without activity in 20 mgm. per kgm. doses were called zero. In addition, the 7-chloro-3-hydroxy-2-methylcinchoninic acid and the 3-hydroxy-2-phenylcinchoninic acid have been found to decrease phenol red excretion when administered orally to dogs. With the former, the effect of 50 mgm. per kgm. was evident at 5 and 24 hours, but was not detectable at 48 hours. With the latter, activity persisted as long as 48 hours after doses of 100 mgm. per kgm.; however, a dose of 30 mgm. per kgm. was ineffective, whereas a dose of 10 mgm. per kgm. shows an unequivocal effect when given intravenously. The 7-chloro-3-hydroxy-2-phenyl-

TABLE 1

The Effect of Cinchoninic Acid Derivatives on the Concentration of Phenol Red by Frog Kidney Tubules in vitro



SUBSTITUENTS	MINIMAL INHIBITORY CONCENTRATION		RATIO*
	Cinchoninic Derivative	Carinamide	
	mM/l	*mM/l*	
8-carboxy-3-hydroxy-2-phenyl	.008 or .004	.125	16 to 32
7-chloro-3-hydroxy-2-methyl	.016 or .008	.250	16 to 32
7-chloro-3-hydroxy-2-phenyl	.016	.250	16
8-carboxy-3-hydroxy-2-methyl	.016	.250	16
6,8-dichloro-3-hydroxy-2-methyl	.016	.250	16
6,8-dichloro-3-hydroxy-2-phenyl	.016	.125	8
8-chloro-3-hydroxy-2-phenyl	.016	.125	8
3-hydroxy-2-phenyl	.031	.125	4
6-chloro-3-hydroxy-2-phenyl	.031	.125	4
6-carboxy-3-hydroxy-2-phenyl	.062	.250	4
3-hydroxy-2-methyl	.100	.300	3
6-methoxy	.08	.150	2
5-chloro-3-hydroxy-2-phenyl	.062	.125	2
3-ethoxy-2-phenyl	.062	.125	2
3-amino-2-phenyl	.062	.125	2
3-hydroxy	.125	.125	1
2-phenyl	.125	.125	1
3-methoxy-2-phenyl	.200	.125	.62
none	2.0	.5	.25
3-nitro	1.0	.25	.25
2-hydroxy-3-methyl	2.0 or 4.0	.3	.15 or .08
3-amino	1.0	.125	.12
2,3-dicarboxy	1.0	.125	.12
2-methyl	1.0	.125	.12
2-hydroxy	>2.0	.25	<.12
2-hydroxy-3-phenyl	4.0	.25	.06
3-carboxy-2-methyl	>4.0	.125	<.03
p-aminohippuric acid	2.0	.125	.06

* The ratio of the minimal inhibitory concentration of carinamide to the minimal inhibitory concentration of the unknown.

cinchoninic acid, 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid and 3-hydroxy-2-methylquinoline-4,8-dicarboxylic acid at 100 mgm.

per kgm. and the 3-amino-2-phenylcinchoninic acid at 50 mgm. per kgm. orally were inactive. All these compounds are effective when given intravenously (table 3).

In table 4 are given data of representative experiments on two dogs comparing the clearances of thiosulfate and phenol red. It can be seen that there is a definite and prolonged decrease in the phenol red clearance following administration of 3-hydroxy-2-phenylcinchoinic acid or 2-phenylcinchoninic acid, but there is no or only a transient

TABLE 2

The Effect of Quinoline Derivatives on the Concentration of Phenol Red by Frog Kidney Tubules in vitro

SUBSTITUENT	MINIMAL INHIBITORY CONCENTRATION		RATIO*
	Quinoline Derivative	Carinamide	
	mM/l	*mM/l*	
3-hydroxy-2-phenyl.....	.125	.125	1
3-carboxy-4-hydroxy....	.5	.125 or .250	.25 to .5
3-hydroxy-2-methyl.....	>.5	.125	<.25
8-carboxy.....	2.0	.250	.12
4-carboxamido.....	>2.0	.125	<.06

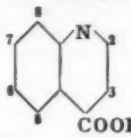
* The ratio of the minimal inhibitory concentration of carinamide to the minimal inhibitory concentration of the unknown.

decrease in the glomerular filtration rate as measured by the thiosulfate clearance. Calculations based on the protein binding found by Grollman (7), Marshall (8) and Shannon (9) reveal that the amount of phenol red excreted after administration of the cinchoninic acid derivatives approximates closely the calculated amount filtered. Marshall and Blanchard (2) have shown that 2-phenylcinchoninic acid is not antidiuretic but that 3-hydroxy-2-phenylcinchoninic acid possesses marked activity. This finding is confirmed by the data in table 4 though the antidiuretic effect of the latter drug is not as great as

would be expected from the dose used. The decrease in antidiuretic effect is very probably due to the presence of a thiosulfate "salt diuresis."

TABLE 3

The Effect of Intravenously Administered Cinchoninic Acid Derivatives on the Excretion of Phenol Red in the Dog



SUBSTITUENTS	EFFECT
8-carboxy-3-hydroxy-2-phenyl	+++*
7-chloro-3-hydroxy-2-phenyl	+++
7-chloro-3-hydroxy-2-methyl	++
8-chloro-3-hydroxy-2-phenyl	++
8-carboxy-3-hydroxy-2-methyl	+
3-hydroxy	+
2-phenyl	+
3-amino-2-phenyl	+
3-hydroxy-2-phenyl ethyl ester	+
3-hydroxy-2-phenyl	+
6,8-dichloro-3-hydroxy-2-phenyl	+
6,8-dichloro-3-hydroxy-2-methyl	+
6-carboxy-3-hydroxy-2-phenyl	+
2-hydroxy-3-phenyl	+
3-amino	0
3-nitro	0

* The effect of 20 mgm. carinamide per kgm. intravenously has been assigned a value of two plus. Compounds which are definitely more active are three plus, those less active are one plus and those with no activity are zero.

DISCUSSION

In the frog kidney slice the appearance of phenol red color in the lumina of the tubules is certainly due to secretion; therefore, the inhibition of this process by certain cinchoninic acid derivatives is powerful evidence that they affect the secretion of phenol red. In the dog our data (table 4) and those of Marshall and Blanchard (2) show that 3-hydroxy-2-phenylcinchoninic acid produces a transient decrease in glomerular filtration rate which is not of sufficient dura-

tion to account for either the antidiuretic effect or the inhibition of secretion. Part of this transient effect may be due to increase in the time required for urine to reach the bladder, but the major factor is believed to be changes in the circulation incident to the intravenous injection of this drug. No such change is evidenced by 2-phenyl-

TABLE 4

The Effect of Cinchoninic Acid Derivatives on the Clearances of Thiosulfate and Phenol Red in the Dog

DOG	PERIOD		URINE FLOW	CLEARANCE		CONCENTRATION IN PLASMA	
	No.	Duration		Thiosulfate	Phenol Red	Thiosulfate	Phenol Red
		min.	*ml./min.*	*ml./min.*	*ml./min.*	*mgm./100 ml.*	*mgm./100 ml.*
H	1	9	4.9	109	115	73.1	0.96
	2	9	4.3	123	124	55.1	1.17
	3	16	3.6	129	135	44.1	1.13
	20 mgm. 3-hydroxy-2-phenylcinchoninic acid per kgm. I.V.						
	4	19	1.0	19.8	38.7	28.8	1.06
	5	16	0.6	116	35.7	19.8	1.24
	6	20	0.8	140	31.9	11.1	1.27
	7	24	0.4	111	33.3	8.8	1.06
B	1	18	5.6	67.5	68.5	70.4	1.20
	2	16	1.1	51.5	69.0	61.3	1.34
	3	32	0.9	48.5	60.7	42.4	1.06
	20 mgm. 2-phenylcinchoninic acid per kgm. I.V.						
	4	12	2.6	68	26.8	23.2	0.89
	5	14	4.2	67	13.2	16.4	0.78
	6	14	5.9	64.5	12.4	14.7	0.60
	7	16	5.7	71.5	16.7	8.8	0.53
	8	13		62.5	15.3	5.0	0.53

cinchoninic acid (table 4). In view of the marked and prolonged decrease in phenol red clearance, it thus seems well established that the effect of these compounds is an inhibition of the renal tubular secretion of phenol red.

It has been shown by Beyer (10) that there are two independent mechanisms for renal tubular excretion one of which characteristically excretes N^1-methylnicotinamide and a second which excretes such

substances as penicillin, phenol red, p-aminohippuric acid and diodrast. Furthermore, it would appear that there are two means of inhibiting the second type of secretion. The secretion of any substance via this route can be inhibited by the presence of another which is also secreted. There apparently is competition for the path of secretion at least in man since Smith, Goldring and Chasis (11) have shown that there is a mutual depression of the clearances when more than one of these substances is present, and the amount of each excreted depends on the ratio of their concentrations. This same secretory mechanism can also be blocked by substances which are not in themselves secreted, e.g. carinamide. In general, much lower concentrations of this type of substance are required to produce inhibition. In the frog kidney slice, for example, (table 1) p-aminohippuric acid shows only one sixteenth the activity of carinamide and in the dog it requires doses of 80 mgm. per kgm. or more to equal the effect of 20 mgm. per kgm. of carinamide. It would appear that 3-hydroxy-2-phenylcinchoninic acid belongs in the non-secreted group since the clearance of the portion of this substance in solution in plasma water is of the order of one ml. per minute (5).

In the frog experiments the use of a known medium into which the drug is incorporated enables one to determine the effect of subjecting the kidney tubules to a known concentration of a drug in the presence of a known concentration of phenol red. Because of the exceedingly small volume of tissue used relative to the volume of the medium the concentrations of the constituents of the medium remain relatively constant. On the contrary, in the dog, the concentrations of both drug and phenol red to which the kidney tubule is exposed are unknown and are altered independently and continuously by distribution, excretion and/or degradation. Considering that such a complicated situation exists one would not expect results in the dog to follow closely those in the frog. However, when these drugs are given intravenously to the dog, the relative order of activity within the series is about the same as in the frog kidney slice with three exceptions. The 3-hydroxy-2-methylquinoline-4,8-dicarboxylic acid, the 6,8-dichloro-3-hydroxy-2-phenylcinchoninic acid and the 6,8-dichloro-3-hydroxy-2-methylcinchoninic acid appear to be considerably less active in the dog than would be expected from the results in the frog.

It is of interest to attempt to determine whether there is any correlation between the antidiuretic activity previously studied (2, 3) in the dog and the inhibition of phenol red secretion. Four compounds, the 2-phenylcinchoninic acid, 3-amino-2-phenylcinchoninic acid, 6-methoxycinchoninic acid and 3-ethoxy-2-phenylcinchoninic acid exhibit no antidiuretic activity yet will inhibit phenol red secretion in the frog in concentrations at least as low as those used for carinamide. The first two named are also active in the dog. On the other hand, no cinchoninic acid derivative has yet been found which possesses antidiuretic activity but does not inhibit phenol red secretion, at least as actively as carinamide.

SUMMARY

Certain cinchoninic acid derivatives have been shown to inhibit the renal tubular secretion of phenol red in frog kidney slices *in vitro* and in the dog *in vivo*. Twenty-seven cinchoninic acid derivatives and seven related quinoline derivatives have been tested on frog kidney slices. The most active, sixteen to thirty-two times as potent as carinamide, were 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid and 7-chloro-3-hydroxy-2-methylcinchoninic acid. Fifteen of the derivatives of cinchoninic acid have been given intravenously to dogs. The most active were 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid and 7-chloro-3-hydroxy-2-phenylcinchoninic acid.

We wish to thank Sara Ann Verplanck and Irene T. Payne for technical assistance.

REFERENCES

1. Dearborn, Earl H.: Inhibition of the appearance of phenol red in frog kidney tubules *in vitro*. Proc. Soc. Exper. Biol. & Med., **70:** 105, 1949.
2. Marshall, E. K., Jr. and Blanchard, K. C.: The antidiuretic effect of 3-hydroxycinchoninic acid derivatives. J. Pharmacol. & Exper. Therap., **95:** 185, 1949.
3. Marshall, E. K., Jr., Blanchard, K. C. and Dearborn, Earl H.: Further observations on the antidiuretic effect of cinchoninic acid derivatives. Bull. Johns Hopkins Hosp., **86:** 89, 1950.
4. Blanchard, K. C., Dearborn, Earl H., Maren, Thomas H. and Marshall, E. K., Jr.: Stimulation of the anterior pituitary by certain cinchoninic acid derivatives. Bull. Johns Hopkins Hosp., **86:** 83, 1950.

5. ZUBROD, C. G., DEARBORN, EARL H. AND MARSHALL, E. K., JR.: The effect of 3-hydroxy-2-phenylcinchoninic acid on the renal secretion of phenol red and penicillin. In press.
6. GILMAN, A., PHILIPS, F. S. AND KOELLE, E. S.: The renal clearance of thiosulfate with observations on its volume distribution. Am. J. Physiol., **146:** 348, 1946.
7. GROLLMAN, A.: The combination of phenol red and proteins. J. Biol. Chem., **64:** 141, 1925.
8. MARSHALL, E. K., JR.: The secretion of phenol red by the mammalian kidney. Am. J. Physiol., **99:** 77, 1931.
9. SHANNON, J. A.: The excretion of phenol red by the dog. Am. J. Physiol., **113:** 602, 1935.
10. BEYER, K. H., RUSSO, H. F., GASS, S. R., WILHOYTE, K. M. AND PITT, A. A.: Renal tubular elimination of N-methyl-nicotinamide. Am. J. Physiol., **160:** 311, 1950.
11. SMITH, H. W., GOLDRING, W., CHASIS, H.: The measurement of the tubular excretory mass, effective blood flow and filtration rate in the normal human kidney. J. Clin. Investigation, **17:** 263, 1938.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

Morbus Caeruleus. Edited by E. MANNHEIMER. 332 pp. $9.25. *Interscience Publishers, New York.*

Morbus Caeruleus, edited by Mannheimer, contains the contributions of 12 workers. It contains chapters on the embryology of the human heart, on clinical and roentgenological examination, on angiocardiography, electrocardiography, on cardiac catheterization and on surgical treatment. According to Professor Lichtenstein, who wrote the introduction to the book, "The aim of this book will be to judge on the basis of our experience the value of the different clinical methods in order to evaluate the results of surgical treatment as far as is possible at this time." In reality, the scope of this book exceeds this outline.

The first chapter contains a discussion of the embryology of the human heart and blood vessels. It represents an excellent outline of this difficult field.

The chapter on clinical examination contains a detailed description of the history, symptoms and signs of patients with the cyanotic type of congenital heart disease. The statement that squatting increases pulmonary function is too vague to explain this mysterious behavior of the cyanotic child. Equally difficult to interpret is the statement, that "when patients with Eisenmenger's Complex squat, the reason may be due to the presence of pulmonary damage". A more specific discussion of these important problems would have been of great value.

The chapter on roentgenological examination by Eek, is one of the best chapters on roentgen technique and examination this reviewer has seen. Of particular importance is the clear description of the roentgenological diagnosis of variations of the aortic arch.

In the chapter on angiocardiography, the authors mention the potential dangers of this procedure.

There is a special chapter on heart tolerance tests in which the hypoxia and the standard exercise tests are discussed. It is of interest that the results indicate that the inhalation of a low oxygen concentration can be tolerated well by cyanotic children. The statistical treatment of the result with the standard exercise test is of great value.

The chapter on cardiac catheterization deals with the details of anesthesia used, and with formulae employed in the calculation of various flows. The pressure tracings are excellent. The reviewer would have liked a more precise definition of physiological terms used. For instance, the term "effective pulmonary blood flow" is never sufficiently explained.

The chapter on surgical treatment of Tetralogy of Fallot by Sanbloom is thorough and well written. The chapter describes pre- and post-operative treatment as well as the complications which might follow operation.

The book contains a large source of material which is well presented. It has both the advantages and disadvantages of a work to which a series of authors have contributed. Its main advantage lies in the fact that the various chapters have been handled expertly. However, it could be more concise and uniform. As a whole the book represents a worthy contribution to a rapidly growing field.

RICHARD J. BING

Clinical Electrocardiography. By FRANCIS F. ROSENBAUM. Edited by HENRY A. CHRISTIAN (Reprinted from Oxford Loose-Leaf Medicine). 373 pp. $4.50. *Oxford University Press, New York.*

This volume, which was written as one of the new chapters in the Oxford System of Medicine, is now being published in separately bound form. Dedicated to Dr. Frank Wilson, the work surveys the field of clinical electrocardiography in a compact well-written essay. The contributions, techniques and interpretations of the Ann Arbor "school" are given full emphasis. Most of the illustrations are reproduced from Wilson's many original papers, and these and some of the text will be familiar to those who have studied those articles. The author has summarized and used the material well, and although there are many controversial aspects which are not dealt with as such, most of what is presented is widely accepted. For the beginner in electrocardiography and for those who would like a rational guide to the newer leads, the volume can be highly recommended as an introduction.

In view of the recent progress in understanding the form of the EKG, it is refreshing to find this subject given a full share of consideration along with the usual section on arrhythmias, which latter subject usually dominates most elementary texts. The author is careful to advise the reader on the limitations of the EKG method of diagnosis and it is difficult to find fault with the good sense of this approach. Up to date material on bundle branch block, infarction patterns and electrolytes is given. The illustrations are quite good and there is a full bibliography.

A. G.

Penicillin. Its Practical Application, 2nd edition. Edited by SIR ALEXANDER FLEMING. 491 pp. $7.00. *The C. V. Mosby Co., St. Louis, Missouri.*

This is a brief, practical compendium of the clinical uses and ways of administering penicillin. It is a strictly British text and is a well written and thought out appraisal by some thirty-five individuals, so that not only is the pharmacology and mode of action of the drug covered adequately, but also each specialty has a representation. Such are the chapters on Penicillin in Ophthalmology, Otolaryngology and Neurosurgery. Included also is a chapter on Penicillin in Animal Diseases, which presents in moderate detail the use of this antibiotic in such varied conditions as bovine mastitis and canine leptospirosis.

There is an outline chapter on Streptomycin and several pages on Chloromycetin and Aureomycin, so that one may see that the second edition of this text has expanded a bit beyond the title. All this is to the good.

This is a text which deserves careful reading by American medical practitioners, for procedure is by no means identical and the evidence for the different procedures, either British or American, is by no means adequate. For instance, the treatment of pneumococcal meningitis is much more radical than usually carried out in this country. "If the infecting organism is found to be the pneumococcus, then it becomes essential to exert every effort on behalf of the patient with this fulminating disease without any delay; the solution is introduced on the first day into the lumbar theca, and the cisterna magna and the ventricles and subarachnoid space of the hemispheres, 10,000 units in each location" (p. 286). In this country there are many who veer away from any intrathecal treatment. Statistically significant differences between the results of two different treatments carried out on two series of cases, which simply were not comparable in the first case, offer no solution to the problem. Yet, in this particular case no indication is given as to the degree of success that accompanies such neurosurgical procedures.

No doubt, each specialist will find points on which to disagree. This will stimulate thought and more careful work. The Mosby Company has performed a service by making this second edition available in this country.

F. B. B.

The Practice of Medicine, 5th edition. By JONATHAN CAMPBELL MEAKINS. 1558 pp. $13.50 *The C. V. Mosby Co., St. Louis, Missouri.*

The progression of the sum of human knowledge is said to be logarithmic with respect to time; so, at least, must be the advance of medicine. There need be no apology, therefore, for the appearance of a new edition of a standard text on medicine. That the task in this case continues to be undertaken largely by one man is a tribute to the experience, wisdom, energy and capacity of Dr. Meakins.

For perhaps more than a decade medical teaching has been moving from morbid anatomy to an appreciation of altered function. There was no need for reorientation in this volume, however, for Meakins has always sought to explain symptoms in terms of physiological response. There is, moreover, increasing emphasis on the responsibility of emotions in disease, culminating in a new section concerned entirely with psychosomatic medicine.

Because it is so much the work of one man, there is a cohesion about the book; and because it is the work of Dr. Meakins the book is readable, stimulating and often provocative. The author's bias is reflected honestly. As is to be expected from Dr. Meakins, the chapters on pulmonary and on cardiac disease are especially instructive. On the other hand, his sweeping polemic against the dogma of electrocardiographic empiricism seems to have betrayed him. Certainly there is little justification for the employment of confusing terminology abandoned ten to fifteen years ago by electrocardiographers. In appealing from electrocardiography to an understanding of cardiac muscle, Dr. Meakins implies incorrectly that the knowledge of skeletal muscle metabolism is applicable directly to cardiac muscle and he presents the abandoned "phosphagen" scheme as relating to the contraction energy of muscle.

Despite the accelerated pace of therapeutic innovation, which must be the sorest trial for any textbook of medicine, Dr. Meakins has managed, in the main, to keep abreast. He discusses the use of vitamin B_{12} in pernicious anemia and indicates that aureomycin shows promise in atypical pneumonia, although a number of observers entertain reservations on the latter score. He mentions the use of BAL in arsenic poisoning but ignores it in the treatment of mercury poisoning. He notes that thiouracil has been used in the management of hyperthyroidism, but does not mention propyl-thiouracil and still advocates surgical intervention as the treatment of choice. An otherwise excellent chapter on diabetes does not discuss the significance of alteration in potassium distribution in the management of diabetic acidosis.

In a volume of this scope, the deflections noted are relatively trivial, but their presence emphasises that the student is well-advised to consult more than one textbook of medicine, Dr. Meakins' among them.

K. L. Z.

A Text-Book of Psychiatry for Students and Practitioners, 7th edition. By Sir David Henderson and the late R. D. Gillespie. 740 pp. $7.75. *Oxford University Press, New York.*

The seventh edition of this standard and widely read textbook of psychiatry retains the form and most of the contents of the previous editions which made it popular with medical students throughout the English speaking world. It remains a useful and very well-written book from which the student can gain an impression of the general field of psychiatry and the various clinical pictures; but, because of the marked changes occurring in perspectives of American psychiatry this text will probably be found to have decreasing usefulness for the American student. It contains the advantages and the very profound shortcomings of combining a Kraepelinean, Meyerian, and Freudian orientation, keeping in the safe middle gound but never offering an integrated approach to psychiatry. For example, the chapter on general psychopathology, which should offer a foundation for most of the remainder of the book, is written largely from a psychoanalytic orientation, presented in such condensed form that it can have very little meaning to the student and would probably only add to his perplexity. The special psychopathology of various conditions discussed in later chapters sometimes stems from this chapter on general psychopathology but just as often utilizes another approach, or offers several divergent views.

The major revision of the book lies in the chapter on psychopathic states, the authors recognizing the inadequacy of present concepts of psychopathic personalities. The revision does not seem to be a particularly happy one; it presents a more generalized classification which may help break down the attempts to categorize psychopathic personalities, but it does not help make them more understandable. A chapter on the psychiatry of childhood is well presented, and it seems to the reviewer that the entire book would benefit if this were not appended at the end of the work as a chapter on a related field, but took a more natural position at the beginning of the volume to serve as an introduction to the development of deviations of

personality formation, upon which later chapters could be based. A chapter is included on the psychoses and the psychoneuroses in war, but rather surprisingly for a new revision of a textbook of psychiatry, there is only passing mention of psychosomatic conditions. The book has more usefulness in regard to the psychoses and institutionalized patients than for anyone interested in the practice of psychiatry where knowledge of the psychoneuroses and psychopathic states is more important than familiarity with description of psychotic conditions. As an example, it can be pointed out that the problem of homosexuality which relates to many other psychiatric conditions receives but a page of the text, and all other perversions of sexuality but a brief paragraph.

In almost all American medical schools there is a trend to integrate the teaching of psychiatry more closely with medicine as a whole, stressing the importance of understanding the personality functions in the lives of all patients to improve treatment of the individual. This book would not tend to lessen the gulf between a psychiatric orientation and a general medical orientation. Then, too, in many schools the various reaction patterns are not considered as such clearly differentiated syndromes as presented here. The book will continue to serve as an excellent reference for that portion of psychiatric teaching in medical schools devoted to psychiatry as a specialty where it is important for the student to gain a picture of what the various syndromes are like.

T. Lidz

The Eosinophil Count in Health and In Mental Disease. A Biometrical Study. By Finn Rud. Translated from Norwegian by Lektor Oskar Sik. 433 pp. Norwegian Kroner $20.00 plus postage 2.15. *Johan Grundt Tanum Forlag, Oslo.*

This book contains a complete review of the literature on eosinophil counts and results of four years of research by the author.

At the onset, the statistical errors involved in the direct estimation of the eosinophil count and the gross errors inherent in the direct measurement are pointed out. Then the author shows the considerable variation in the eosinophil level of the same individual from season to season, from month to month, from day to day, from hour to hour and from minute to minute. He has shown that there is a tendency for the eosinophil level to rise during the day time unless the individual has fasted in which case there may be a fall in the count. There was no systematic change during exercise.

Among the cases studied in mental institutions, the author found a relatively low instance of allergy among schizophrenics and manic depressives. On the other hand, he found a higher than normal occurrence of allergic individuals in the neurotic group. The average eosinophil level in the schizophrenic and manic depressives was lower than normal, and the average count in the neurotics with the higher instance of allergy was greater than normal.

Small doses of sedatives had no effect on the eosinophil level, although there was a marked fall when the sedative produced any disturbance such as nausea and

vomiting. Cardiazol, electric shock, insulin shock, etc., caused a prompt and marked fall in the eosinophil level. A fall was also noted after epileptic attacks or migraine seizures.

This study was published in 1947 and, despite the fact that this antedated the ACTH era, the book is of considerable value to those working in this field.

ROGER A. LEWIS

Primer of Allergy, 3rd edition. BY WARREN T. VAUGHAN. Revised by J. HARVEY BLACK. 175 pp. $3.50. The C. V. Mosby Co., St. Louis, Missouri.

This small volume on allergy, now in its third edition, was written originally by the late Dr. Vaughan for the lay patient afflicted with one or more manifestations of allergy. Dr. Vaughan felt that a definite need existed for a treatise on allergy written in simple, non-technical language which would provide patients with sufficient insight into their allergies to encourage their cooperation in the common effort to control their troublesome symptoms. The second edition, revised by Dr. Vaughan in 1945, contained a new chapter "Learn to live with your allergy", which was originally published in the magazine LIFE AND HEALTH. Dr. J. Harvey Black, who revised Dr. Vaughan's book on allergy, has also revised this edition.

The nature of allergy, the known specific causes of the several commonly recognized allergic syndromes and the corresponding diagnostic and therapeutic procedures, including desensitization and results of treatment, are discussed. Questions which patients might ask concerning their allergies and answers thereto conclude each of the several chapters. General directions, including food elimination diets, to patients, depending on the particular allergic manifestations they present, complete the volume. Much emphasis is placed on "sticking" to a therapeutic regime and not getting too discouraged if the response to treatment is slow, even if symptoms persist for months and even for years. Dr. Vaughan was a facile and prolific writer, and though the text in this volume is pleasant reading, there is considerable rambling and much repetition. The attempted explanation of the state of allergy is somewhat metaphorical and confusing and, in the opinion of this reviewer, this chapter would be more readible and comprehensible if stated in definite, simple terms. Food sensitivity as in Dr. Vaughan's textbook is emphasized as the major etiological cause of various allergic reactions. There is considerable debate about this in most informed circles. Unfortunately, there is no discussion of drugs, such as ephedrine, adrenalin, and more recently, the antihistaminic compounds which would enlighten the patient with regard to therapy. The book, however, despite its drawbacks has been popular and if read by the individual patient would fulfill the author's objective to a considerable degree and would undoubtedly save the physician many a minute in answering numerous questions, although most patients still prefer getting most of their information concerning their difficulties directly from their own physician.

WALTER L. WINKENWERDER

Postgraduate Gastroenterology. Edited by HENRY L. BOCKUS. 670 pp. $10.00. *W. B. Saunders Company, Philadelphia, Pa.*

Under this title Dr. Bockus has assembled a number of excellent papers given in Philadelphia at a week-long refresher course in gastroenterology in December of 1948. Naturally the book doesn't contain all information to be found in its editor's monumental three-volume work. But it presents adequately, and usually in an interesting manner, the more recent advances and the controversial subjects in the field of gastroenterology. Most of the material was originally given as symposia and the subjects have been similarly arranged in the book. Short periods for questions followed each symposium and the answers to these questions haven't always been complete. Thus the reader has the urge to remain after "class" to ask more questions. For example, after the psychosomatic aspects of cardiospasm have been discussed, the speaker concluded, "It would appear that the phenomena of oesophageal hypermotility and cardiospasm occur as a part of a biologic pattern of defense, etc." Nothing was said about the treatment of cardiospasm. A questioner asked, "Do you prefer to treat cardiospasm by psychotherapy as opposed to other methods of treatment?" The reply was very general, too general to satisfy your reviewer. It was, "If there is evidence that situational conflicts are relevant to the development of this or that bodily disturbance, therapy should involve consideration of the life situation and attitudes of the subject. If other factors appear to be of special importance, they should be dealt with. No therapy need be used to the exclusion of some other approach." How your reviewer wanted to heckle the lecturer with, "What about dilatations of the cardia!"

The subjects discussed included oesophageal disorders, gastric secretion, gastric neoplasms, recent contributions to the knowledge of peptic ulcer and its treatment, the psychosomatic side of gastroenterological problems, gastrointestinal allergy, pancreatic disease, hepatic disease, chronic enteritis, intestinal obstruction, the so-called "postcholecystectomy syndrome," chronic non-specific ulcerative colitis, and carcinoma of the colon. In the course of the lectures clinical cases were presented and discussed on three occasions and these clinics are well reported.

The book, as its title states, is not for undergraduates. The entire section on psychosomatic ailments must be read judiciously and in the light of experience. And so must be read the paper by a surgeon on "Newer Developments in Surgery of the Thoracic Oesophagus," the one on lysozyme in ulcerative colitis and on antilysozyme therapy in that disease, and the one on "Abdominal Symptoms of Allergic Origin." These are good papers but the reader may find himself saying, "Is that so? I haven't noted that nor have I found this or that operation to be necessary."

The talks by Dr. Franklin Hollander on "The Secretion of Gastric Mucus in Health and Disease" and that of Dr. Arthur Finkelstein on "The Roentgen Diagnosis of Gastric Tumours" were especially interesting and informative. After reading Dr. Seymour S. Kety's "The Physiologist's Concept of Biliary Dyssynergia," one may begin to believe that there may be a postcholecystectomy syndrome which does not have a psychic basis. The symposium on pancreatic disease is wonderfully good!

Dr. Bockus' book might be called "What's Going On in Gastroenterology" and no mature physician who is interested in that field will be disappointed in this collection of papers.

J. T. H.

A Primer for Diabetic Patients, 9th edition. By RUSSELL M. WILDER. 200 pp. $2.25. W. B. Saunders Co., Philadelphia, Pa.

The revision was made to enable the book to conform to the current trends for more liberal diets and less close restriction of diabetics regulated with insulin. A few other minor changes were made; the index was altered some and improved for reference thereby. Rewording of the text in several instances has resulted in increased clarity; the formats for several of the tables have become more presentable with figures printed in larger type. The substitutions and recipes chapter has been expanded. On the whole, the revision is useful and fully abreast of present concepts of diabetes.

B. P. F. JR.

Letters of Jean de Carro to Alexandre Marcet, 1794-1817. Edited with an Introduction and Notes by HENRY E. SIGERIST. 78 pp. $2.00. *The Johns Hopkins Press, Baltimore, Md.*

The story of the gradual introduction of the practice of inoculation of man with matter originally obtained from cows (vaccination) to take the place of variolation is a fascinating one the world over. Jean de Carro is most famous for his efforts in introducing this procedure into the Continent from England. Many of his letters to his friend, Marcet, who was trained and practiced medicine in England, tell of his attempts to vaccinate; of his successes with dried threads impregnated with pus from an individual patient's pock in England, and of occasional failures with moist material sent inside feather quills. One of de Carro's patients insisted on vaccination only with such threads sent from England, but de Carro had only an old one sent to him some seven months previously and remaining in a warm room. He used this and it worked.

The medical world was full of the discovery of the century. Would continual transfer of cowpox from man to man make it more virulent for man? Cases of smallpox did arise in a hospital where vaccination was carried out. de Carro rightly suggested that this was due to contamination with the virus of smallpox. There was continual debate as to the origin of cowpox. Was it transferred from a disease of horses called "Grease?" Did it really protect against smallpox? This question was frequently tested by inoculating the vaccinated subject with variola minor after vaccination, and deCarro also carried out such tests.

Jean de Carro was not to be left behind in the struggle for fame and when vaccination was no longer a novel and exciting thing, he turned to new inventions such as sulfur fumigation chambers for the treatment of skin diseases and exploited this for a while. Thus his letters are revealing of many facets of medical practice starting with the early days of medical school, on until late in life. Dr. Sigerist has furnished us with a delightfully edited story of the times.

F. B. B.

BOOKS RECEIVED FOR REVIEW

Adrenal Cortex. Transactions of the First Conference, November 21–22, 1949. Edited by ELAINE P. RALLI. 189 pp. $2.00. *Josiah Macy, Jr. Foundation, New York.*

Clinical Electrocardiography. By FRANCIS F. ROSENBAUM. Edited by Henry A. Christian. (Reprinted from Oxford Loose-Leaf Medicine). 373 pp. $4.50. *Oxford University Press, New York.*

Clinical Orthoptic Procedure. By WILLIAM SMITH. 393 pp. $8.00. *The C. V. Mosby Co. St. Louis, Missouri.*

Die Gewebsmastzellen im Menschlichen Knochenmark. The Klinisch-Haematologische Bedeutung Bei 20 Aregen Erativen Anamien. By P. BREMY. 78 pp. DM 7.20 ($1.70). *Georg Thiem Verlag, Stuttgart.*

Essentials of Ophthalmology. By ROLAND I. PRITIKIN. 567 pp. $7.50. *J. B. Lippincott Co. Philadelphia, Pa.*

Human Milk. Wartime Studies of Certain Vitamins and other Constituents. Medical Research Council. Special Report Series no. 269. By S. K. KON AND E. H. MAWSON. 188 pp. 4 shillings net. *His Majesty's Stationary Office, London.*

Human Sterilization. Techniques of Permanent Conception Control. By ROBERT LATOU DICKINSON AND CLARENCE JAMES GAMBLE. 40 pp. *Waverly Press, Inc., Baltimore, Md.*

Humanism in an Age of Science. A Ludwig Mond Lecture delivered at the Manchester School of Medicine, October 6, 1949. By JOHN FARQUHAR FULTON. 26 pp. 75 cents. *Henry Schuman, Inc., New York.*

Letters of Jean de Carro to Alexandre Marcet, 1794-1817. Edited with an introduction and Notes by HENRY E. SIGERIST. 78 pp. $2.00. *The Johns Hopkins Press, Baltimore, Md.*

Klinik und Therapie der Massiven Magendarmblutung. By NICOLA MARKOFF. 135 pp. Fr. 14.20. *Grune & Stratton, Inc., New York.*

Le Probleme du Cancer. By FRANS DAELS. 189 pp. 7 francs. *L'Effort Humain, Geneve (Suisse).*

The Management of Obstetric Difficulties, 4th edition. By PAUL TITUS. 1046 pp. $14.00. *The C. V. Mosby Co., St. Louis, Missouri.*

The Mask of Sanity, 2nd edition. By HERVEY CLECKLEY. 569 pp. $6.50. *The C. V. Mosby Co., St. Louis, Missouri.*

Medical Diagnosis. Applied Physical Diagnosis, 2nd edition. Edited by ROSCOE L. PULLEN. 119 pp. $12.50. *W. B. Saunders Co. Philadelphia, Pa.*

Nutrition in Health and Disease, 11th edition. By LENNA F. COOPER, EDITH M. PARBER, HELEN S. MITCHELL. Assoc. Author, HENDERIKA J. RYNBERGEN. 744 pp. $4.00. *J. B. Lippincott Co., Philadelphia, Pa.*

Psychosomatic Medicine. Its Principles and Applications. By FRANZ ALEXANDER (with a chapter on The Functions of the Sexual Apparatus and Their Dis-

turbances. By THERESE BENEDEK). 300 pp. $4.00. *W. W. Norton & Co., New York.*

Textbook of Endocrinology. Edited by ROBERT H. WILLIAMS with the collaboration of PETER H. FORSHAM, HARRY B. FRIEDGOOD, JOHN EAGER HOWARD, EDWIN J. KEPLER, WILLIAM LOCKE, L. HARRY NEWBURGH, EDWARD C. REIFENSTEIN, JR., WILLIAM W. SCOTT, GEORGE VANS. SMITH, GEORGE W. THORN AND LAWSON WILKINS. 753 pp. $10.00. *W. B. Saunders Co., Philadelphia, Pa.*

A Textbook of Gynecology, 6th edition. By ARTHUR HALE CURTIS. 799 pp. $10.00. *W. B. Saunders Co., Philadelphia, Pa.*

A Textbook of Psychiatry for Students and Practitioners, 7th edition. By SIR DAVID HENDERSON and the late R. D. GILLESPIE. 740 pp. $7.75. *Oxford University Press, New York.*

Tissue Culture Technique. By GLADYS CAMERON. 191 pp. $4.20. *Academic Press, New York.*

World Surgery. By STEPHEN A. ZIEMAN. 181 pp. $6.00. *J. B. Lippincott Co., Philadelphia, Pa.*